RESEARCH AND CLINICAL MEDICINE *

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NO-ONE will deny that we need more research, not as a substitute for good teaching and clinical medicine, but as an essential component of these activities. What are the reasons for this? Firstly, medicine now moves so rapidly that many procedures which were considered "pure" research a few years ago are now essential to modern investigation and treatment. If there is no constant background of research, then these procedures are simply not understood or available and investigation and treatment become outdated. Adequate concepts and highly specialised techniques cannot be evolved overnight, and without this constant background of research and its application leadership is lost.

A school's reputation now largely depends on the level of the research there. Under the modern system of patronage, the dispensation of funds for improved clinical facilities as well as for research is closely geared to this reputation. The standard of research can be judged by harsh and accurate criteria, and there is no easy way round. Thus research is not only desirable but necessary even on the most uninspired practical grounds. I would commend these considerations to those who will support the release of endowment funds only for matters related to the immediate clinical amenities and treatment of patients. Endowment funds are a fortunate heritage of many teaching hospitals. It is our duty to see that these funds are spent on developments, particularly in research, that should distinguish a great medical school from a non-teaching hospital. It is a weak and short-sighted policy to spend this money to provide reasonable and essential clinical facilities and amenities. Although these are an absolute necessity, if they are substandard then the appropriate hospital board is responsible for their improvement and should be pressed hard to meet their fair commitments so that the endowment funds are available for their proper purpose.

In this fast-moving world, new talent is the most valuable commodity: it is the very currency of progress; yet it is still often discouraged and wasted, although in all conscience there is little enough of it. Edinburgh can no longer afford to export an excess of young talent. "Export" is somewhat of a euphemism as many had no choice but so seek their careers elsewhere. When we speak proudly of the Edinburgh men who leave and make great names elsewhere, we must also be really satisfied that those who remain measure up to them. The recruitment of this talent is therefore a most important local and general responsibility. Teachers must be on the constant lookout, and remember that young talent does not always conform easily to the accepted pattern of study and behaviour.

The Academician and the Part-timer

The demands of modern medicine are so great that we must reassess the difficult problem of how much time physicians and surgeons in medical schools can devote to activities outside the hospital and medical school. Is it possible to run a large private practice and remain a leader at the head of modern advances? Please do not think that I am being critical of my part-time colleagues or the many teachers to whom I owe so much, or of the principle of private practice. We must remember that almost the whole burden of maintaining medical advancement and of medical teaching has been borne by the so-called part-timer until recent years. His contribution to modern medicine and teaching are still enormous, although there has been a sharp fall in original observations from this source. This is because the scientific background and complexity of modern medicine has become so great, and advances follow each other so rapidly, that even the most brilliant and industrious men just cannot spend almost half their working time away from the hospital and medical school and maintain a modern standard of investigation and research as well as of treatment. It is jokingly stated that if you go away for the weekend you are out of date on Monday, and there is an element of truth in this. I think that it is extremely important to British medicine that the part-timer in the medical school should have the opportunities and facilities to work for longer periods in their hospitals without the great sacrifices of finance and even of health that some now make. The whole matter is bedevilled by complicated financial considerations, but the powers responsible should see to it that these do not threaten the standards and efficiency of teaching hospitals.

The system whereby consultants can carry out limited sessions of private practice in appropriate suites provided by the hospital has much to recommend it. This will particularly enable the younger consultant to keep the wolf from the door at a time when he has to house and nurture a young family, without excessive distraction from his main task of hospital clinical work, teaching, and research during his formative years.

The academician must make an equal effort to restrict his extramural and extra-academic activities. Our system threatens to become a remorseless machine to neutralise and sterilise the academician and part-timer alike. The weight of administrative responsibility has become quite excessive. These activities should be carried out mainly by men who are paid to administer, and thus allow medical men to spend more time practising their own profession. The medical profession has accepted, and sometimes even sought, this heavy load in order to protect their patients and themselves from the possible threats of a new bureaucracy. I feel this aspect has stabilised reasonably and that the time has come when the profession should be able to select appropriate men, who are fully salaried, to represent them in these matters.

Many Government organisations rely almost exclusively on medical leaders and academicians for expert opinions on a multitude of subjects of great public interest. These men may fairly feel that such commitments do credit to their university or medical school as well as to themselves. Yet it is impossible to defend a system whereby the more senior and eminent a man becomes, the more rarely is he seen in his wards and laboratory. Too much is demanded of too few. Many of these tasks could be performed by

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appropriate men of talent who should be paid on a full-time basis. Indeed this would give us a little more room at the top and those at the top a little more time to do their appropriate tasks.

Again, modern methods of travel have made visits all over the world feasible if not always desirable. The exchange of ideas is excellent; but without a genuine background of hard, unremitting work such activities can become a sterile habit. How many of us have heard the same people and the same ideas in places thousands of miles apart? Although I fully support reasonable liaison between medical and scientific workers all over the world, a good library and the capacity to select and read quietly and critically is certainly a far more efficient method than forever travelling, distracted by exhaustion, changing scenes and climates, and relentless hospitality.

The academician's tasks lie mainly in the ward, at his desk, and in the laboratory. Although he may become busier every day, unless he is working in these places, then, as an academician, he is truly becoming idler.

Professorial Units

The first responsibility of any doctor, no matter where he is or what he is doing, is the proper investigation and treatment of those patients who rely on him for their care. The professorial units are fortunate in this respect in so far as they have a considerable extra number of lecturers and fellows on their staff. Almost all the staff work on a full-time basis. This allows the most careful and detailed supervision of patients and yet leaves adequate time for learning, discussion, and research. This happy blending of clinical work without excessive hurry and pressure with the opportunity to study specific problems in the ward, library, seminar room, and laboratory is ideal for the development of young professional men of energy and ability. The long and attractive lists of candidates for such appointments as compared with the meagre applications for the more routine junior clinical appointments leaves no doubt what the younger generation need and want. It is, however, constantly necessary to reaffirm that first-class patient care is the keystone of good medicine and that without it no medical organisation can justify itself. Medical professorial units have a particular responsibility in this respect. They must show, so that none can doubt, that increased research and scientific activity really means improved patient care. British medicine still has the highest standard of history-taking and careful physical examination. This, when blended with a natural compassion for one's fellow men and a sympathetic understanding of their faults, weaknesses, and even their virtues gives British clinical medicine a unique bedside efficiency and quality of which we should be very proud.

Some members of our profession appear to genuinely believe that research is incompatible with efficient, compassionate medicine. Throughout my career, although I have never stopped clinical work, except in war-time, I have been asked: "Do you actually treat patients?" After some initial irritation I have come to consider such inquiries naïve rather than hostile. Yet one cannot help feeling that if many medical men of considerable influence hold the view that a man who has done original work is probably not a good clinician, then they are fundamentally opposed to research. It is our duty to see that the next generation of doctors do not have this view.

There are, of course, other difficulties in the organisation of academic medicine. The increasing attraction to these units causes a large accumulation of men who cannot possibly all advance steadily up the academic ladder. It would be absurd to suggest that everybody can succeed at everything, but we now have a group of talented men who have proved themselves over and over again and yet are unable to obtain more senior appointments which they richly deserve. Again, competition is always healthy, but frustration of true endeavour and talent must have a constant deleterious effect on the younger generation, particularly as these are now accustomed to a higher standard of living and, although still willing to take risks and make sacrifices, expect some reasonable opportunities and reward. A number of these men emigrate; others apply for and obtain part-time or full-time consultant posts and will enrich medicine wherever they go. Yet they know that in almost all instances they will have no or little opportunity for research. Further, such appointments often cause resentment among those who have followed the older, more traditional, path of advancement. I will return to this point.

Non-academic Units

As we have seen, the environment in the professorial units is, at least potentially, satisfactory and good medicine and research are feasible and usually practised. What of the non-professorial areas of the hospital? How can they deal with the modern challenge? I have already inferred—I hope without offence—that in a medical school all consultants should be qualified to supervise and conduct research as well as practise clinical medicine and teaching. At present, few part-time chiefs have the time or the facilities to do this. A minority make superhuman efforts despite all difficulties, and succeed in making original contributions. One wonders how much more they would have done given the proper time and opportunities.

It is a most unfortunate state of affairs that some hospital boards consider that the non-academic units in teaching schools should have a bare minimum of junior clinical staff as in non-teaching hospitals. These younger men are fully committed to ad-hoc day-to-day clinical work and have neither the time nor the facilities to initiate any research activity. Again, a few do the almost impossible and carry out research with academic and financial support from elsewhere, although they often have to go round with cap in hand for a long time to achieve this. The majority, however, never develop or soon lose the desire to contribute. Without stimulus or opportunity they may become mesmerised by their everyday activities and think in terms of career without new endeavour. Young men must not, and I believe do not want to, think that the ladder to success is merely cramming for the membership or fellowship, arriving early in the morning with a clean collar and doing ward rounds, sitting through endless clinics, and presenting interesting cases to appropriate audiences.

As I have mentioned, there is inevitably some friction and ill-feeling in the competition for appointments between such men and those with academic training. This is a great pity as neither group is to blame. There is no reason why all doctors holding junior posts in a medical school should not have the same opportunities to become good clinicians and do investigative work. A number will eventually find that they are more suited for full-time clinical work and a minority that they are able and anxious to continue in research as well as clinical work.

Reverting to the problem of the hospital staffing structure, I feel that the National Health Service has placed itself on the horns of an odd dilemma. On the Appointed Day it was obvious that the National Health Service would radically alter the whole of the conditions of both hospital and private practice. Yet a somewhat rigid bureaucracy was faithfully built on the old hospital system, with all its anomalies, which was suited to the pre-Health-Service era. Thus the National Health Service administration in large hospitals is unintentionally perpetuating many arrangements which were evolved over thirty years ago and are entirely opposed to the trends of the National Health Service and modern medicine. Appeals for strict conformity with the administrational machine usually come from the conservative rather than the progressive. It is high time that this "auto-obstructionism" was resolved by more appropriate staffing and administration.

In order to provide the proper opportunities for younger medical men in the non-university areas it is essential that there should be more appointments to the junior and middle grades in teaching hospitals and that all non-professorial charges or firms should also have laboratory facilities for special investigations and research.

There are of course a number of difficulties, but none are insurmountable. The first is money. The hospital boards are under considerable financial stress. Yet the extra appointments I would suggest are in the £700–1200 salary bracket. Thus each charge could have this vital improvement of staff for £2000 a year. The laboratories are a necessity anyhow, and I am sure that all those in the university would help with whatever facilities they could if they were asked to do so. A great deal of laboratory apparatus and space is often used for less than 20% of the time, and several charges could share laboratory facilities. Big routine biochemistry laboratories have almost reached a maximum. The day of " chit " research is over and we need more biochemists nearer to the patients and working in smaller laboratories alongside the younger clinicians with their clinical problems and investigations. In the same way the biophysicists must not be isolated and not only advise but also work closely with these clinical units.

Perhaps the rearguard will consider that these increases in personnel and research I have suggested are university activities and that the university wishes for a further extension of influence and power. Yet the university has equally heavy demands on its purse and personnel. Modern technology and the non-medical sciences are demanding a larger proportion of the university funds in this intensely competitive industrial age. I would personally welcome the development of more research outside the strict university area. It is both economically and professionally desirable. There are funds available from many non-university sources, and the hospital boards and the Ministry and Department of Health have a defined responsibility to see that the whole of their medical schools are suitable for the development and practice of modern medicine where young doctors as well as students can be properly equipped for the future.

It may also be said that this scheme may increase the number of frustrated young academicians and non-academic registrars. This is not true, as these men will be young and consider their research activities as part of the proper training of a modern doctor whether they are to be practitioners in the National Health Service, in the Colonial Service or Armed Forces, in public health, in industry, or in academic medicine.

Student Selection and Training

Despite the increased care given to selection of students, there is little doubt that the number of outstanding intellects in each year is less than before the war although the average performance is far better. It has been suggested that the present careful selection of " tidy young citizens " eliminates not only the lazy, dull, and unreliable but also some students with great potential promise. I find this difficult to believe. Modern pure and applied sciences, the technologies, and industries are now wide and attractive fields often offering greater rewards at an earlier age. Further, the leaders in these fields—particularly in industry—are hard-headed men who know that talent is spreading thinner and thinner over the increasing number of human activities and that it must be sought out and given attractive and rewarding openings. We in medicine must do the same. We must make our system less feudal and rigid, and not only tell the younger generation how exciting and rewarding a medical career can be but also take steps to see that this is really true.

There is now increasing objective evidence that even at the relatively early age of student selection the most valuable criterion of future performance is the previous record in competitive examinations. Good examination results in good examinations indicate a capacity to work and a reasonable or even high intelligence. Many schools throughout the world are selecting students entirely on the results of pre-university examinations, no matter what the subjects, provided there is a satisfactory report on character; and they are increasingly pleased with this system. Although it is only human to wish to sight and talk to the candidates, there is no doubt that the interview system is extremely time-consuming and very unreliable.

Having attracted and selected our students, what of their medical education? It is often said that this country has more brilliant new ideas about student teaching and practises them less than any other country in the world. We must not forget that the most essential component of learning is plain hard work, and it behoves us to remind the student of this not infrequently. Further, we must not organise the whole of medical education as if every student is a potential Nobel prize winner. Opportunities must be made for the students of great ability; but we must provide, and take great care over, a suitable general programme for the large majority of average students. We must also remember, however, that the now familiar claim that the majority of students will become general practitioners, and that our main task is to provide them with the appropriate education, is no longer valid. Only about a third of students become general practitioners, and this figure is still, I believe, falling.

The detailed teaching of the basic sciences of medicine is being increasingly attacked. Yet, provided the teaching of these subjects is constantly revised and pruned to modern standards, they should still be the foundation stones of medical education. Two years is, in all faith, little time in which to learn the vastly complex structure and functions of the human body. Many laymen would dearly love to acquire such knowledge, and yet some people seriously think that the modern medical student is hard put upon to be subjected to this brief intellectual discipline. If there is any sense of vocation in the students it should be a revelation as well as a discipline.

It has been suggested that only knowledge which is

immediately applicable to the understanding of disease should be taught. This would be truly catastrophic, as it would make teaching and knowledge even more rigid and prevent the planting of new ideas in new minds. There is also an increasing trend to show the students more of the clinical diseases and problems at an early stage. I feel that this activity must be very limited as it may obscure the fact that there is the serious apprenticeship of learning the structure and functions of the human body. Early medical education must not become a series of clinical *hors d'œuvre*. Clinical material can be used to highlight and clarify physiological and anatomical knowledge and principles but not constantly presented like a carrot under the donkey's nose. The students are certainly not donkeys, and they already have a both stimulating and heavy diet. Rather than see clinical medicine brought to the early years, I would suggest that if practising doctors contributed to the teaching of anatomy and physiology (as was done in the past century) and this teaching was continued and woven into the clinical years, then the student would be really convinced that these subjects are the very fabric of medicine. The high records of Cambridge and Oxford may well be partly due to the fact that the hospitals in which their students will eventually learn and practise clinical medicine are geographically and psychologically far away, and that these young men can study and learn and enjoy their basic sciences without the constant distraction and challenge of their future clinical years hanging over them.

The routine lecture has also been attacked by many educationalists, some of whom also wish to get rid of textbooks as well. I personally feel that there is little point in students coming to a university unless they can hear their teachers expound on their subjects. If these lectures are losing their value, then this may be the fault of the lecturers. The lecturer who produces almost the same lecture year after year is not performing his task adequately. In these days when most students can buy textbooks and all can see them in the library, one can well afford to reduce the routine factual flavour of lectures and spend more time on concepts and attitudes of mind. More discussions should take place between the lecturer and the students. The modern student is less violent, more courteous and consistently sober, and, provided there is a mutual feeling of friendliness, this can be done with quite large groups. We must also treat the student as a responsible adult in his later years and let him decide which lectures are valuable to him rather than make them compulsory. Many of us wish that we could charm and captivate an audience, but this gift is for the few. Further, no matter how inarticulate and shy a man may be, he may, in a subtle way, give something to his audience that lasts longer than he or they ever dream of. Smaller tutorial classes, where the teacher and each individual student can discuss various subjects and lose the lecturer-class relationship, are of very great value. Their feasibility is a direct function of the size of the staff. If the staff is too small, then these men may not be willing to sacrifice their few precious hours left for research and this important tutorial activity is neglected. Fortunately the student clinical ward-rounds help greatly in this respect in the later years of the clinical course.

Good textbooks are exceedingly rare, but it is a fact that cannot be escaped that students, whether they are dull or bright, need some relatively simple skeleton of knowledge, no matter how imperfect, to help organise the thousands of facts and fancies they encounter during their education. It is now generally agreed that a series of smaller books written in a more stimulating and less didactic manner on the various aspects of medicine is a great necessity. The new generation of academicians who have now matured are beginning to write such books, and more trouble should be taken to select and recommend those of value to the students, particularly to those of greater ability.

There is little doubt that the ingestion of large amounts of factual knowledge is often a greater burden to the student with the high intelligence quotient than to his more modestly endowed colleague. The selection of the brighter students for a year's honours science degree course in the middle of their main medicine course, as practised in Edinburgh and a number of other universities, is an ideal method of stimulating and inculcating these men of the future with scientific as well as clinical interests. It is also most encouraging to see that in Edinburgh such students are not submitted to another intense course of factual learning but are allowed to pause and look around them and use their exhausted association tracts for thinking rather than memorising. They are also taught some of the meaning of scientific discipline. They learn that absolute certainty is not wisdom but stupidity. The barriers of seniority largely disappear in this environment and respect for persons will replace respect for positions. This is such an important and vital year for these men that it is tempting to suggest how it should be further organised. Yet excessive organisation would destroy its value—a fact that Cambridge and Oxford have long realised. I would like to make one suggestion. Clinical science has in recent years achieved sufficient status to make it worth seriously considering whether some of these men should be allowed to take a degree course in some aspect of clinical science. Naturally they will still be taught a great deal by the "purer" scientists, but some association with fundamental work on particular aspects of disease will allow them to see their clinical teachers in another light and may lay the seeds of important future work.

I will say only a few words about the final clinical years. There is general agreement that, with present trends, the medical student can only see the patient as a vague and almost theoretical figure behind a forest of complex medical education. Each new discipline needs more and more time in the curriculum. Many hospitals are now unintentionally more hostile to the student who senses this and may escape from it, with a free conscience, to lectures, special courses, and more reading. If the intermediate clinical staff also wish to devote their full time to clinical work there is no longer the smallest niche for the student. The clinical student must be integrated once more into routine ward clinical practice. This may give the young doctors a little more time for thought and research. A number of students have resolved this difficulty by becoming ward orderlies during their vacation. Such students return with a greater enthusiasm and appreciation of the exciting and responsible careers in front of them.

The final examinations are a vast subject in themselves. I will only say that it is also a university degree, and some attempt should be made not only to determine the fitness of the student to practise medicine but also to judge his intellectual calibre and grant an appropriate grade of honours. If this were done carefully, the problem of the membership and fellowship (which I will discuss later) would be largely resolved.

The Young Graduate

The student, having passed his finals, is lightly touched by the cap of his Chancellor or Principal and is then almost abandoned for the rest of his training. The medical graduate is required to serve in recognised house-posts for another year before he is considered fit for independent medical practice. The selection of the men and women for these posts is at present poorly organised. Although it is only fair that a consultant should have the final word in the selection of his housemen, some of these appointments, which may affect a man's whole career, seem little related to proven ability.

Let us consider what happens when the graduate becomes a houseman, usually to a large ward or even wards. He is immediately burdened down with an intense responsibility to each patient under his care. He is vastly preoccupied with measuring reality against theory. He has human lives resting on his decisions and is no longer merely trying to placate an examiner. He must learn the art of liaison with his nursing staff, his registrars, and his chiefs, all of whom wish to carry out an unending series of rounds, usually on the same patients. The giving of transfusions, electrolytes, and common but powerful drugs are all new challenges. Admission day finds him attempting to make many decisions which are sometimes beyond his years and experience, while at the same time he must continue to look after the gravely ill patients in the ward—a double burden which increases as the day goes by. This is growing up with a vengeance, and is far too much for the average young doctor. He can rarely fulfil all these duties adequately unless he is a mixture of athlete and intellectual commando. He is being employed more than educated. It is a tradition in many British schools that these young men must be allowed reasonable freedom and direct responsibility to their chiefs and that the senior house-officer and registrar must not interfere unduly, unless directly asked to do so or unless obvious errors are being made. I feel that this tradition is not without danger. Many men rapidly learn that, although you are dealing with human lives, a certain slickness and capacity to avoid the more obvious errors will carry them through this initial period. The sense of apprenticeship may vanish for ever and expediency become the watchword.

How can this unfortunate situation be avoided? I would suggest that the teaching schools should at least double their quota of housemen, who will then have the proper time to really study their patients, to know their diseases, their personalities, their environment and problems in proper detail. They will discover that there is more to be learnt in a few carefully studied patients than in a frenzied round of an oversized parish. The doctors of intermediate grade should work more freely with them so that they increase both the houseman's stature and their own. The houseman has too much clinical responsibility and the final-year student too little. These final-year students should be incorporated more into the immediate bedside clinical responsibilities, and the houseman should have the time to supervise, guide, and help them. The extra money needed for doubling the housemen would be well worth while from the educational point of view alone and could, perhaps, be partly a university commitment. Further, if the houseman is under less pressure he will have time to attend special investigations and procedures on his patients. This is the stage at which he should be able to go to the library and have time to really think about the many diseases that still maim and kill without hindrance. Universities and teaching schools have a great responsibility to these young men and women which is at present largely ignored.

Let us move on to the senior house-officers and the registrars (although the former appears to be a very rare bird in Edinburgh medicine). These doctors live in a very difficult world. In some schools they must not encroach unduly upon the houseman's duties or responsibilities to the patient. Any comment they make by the bedside must not belittle the houseman or highlight any episodic obtuseness of their chief. At the same time they must be ready to deputise for consultants in all capacities, often for long periods. Unless they are on an academic unit, facilities for research are usually non-existent. Besides, there is hanging over them night and day, the black cloud of the membership or fellowship. They know that these examinations are largely cram examinations wrapped in an evasive veil of lifemanship. They may be greatly interested in some challenging problem, but the thinness of the clinical staff and the preoccupation with these examinations gives little opportunity or encouragment. These young and active brains, that should be already attacking the many unsolved problems of medicine and surgery, will be sitting in rooms reading how cowsheds should be kept clean or studying the minutiæ of electrocardiographic changes. I do not wish to belittle either of these important subjects; but this extension of sixth-form know-everything, know-nothing type of learning into professional men's lives up to their late twenties and early thirties is a truly disconcerting feature of British medicine. These men have already spent six or more years under constant supervision and have undergone many exhausting and thorough theoretical and practical examinations. After this they have worked with consultants of acknowledged status. Surely there should be enough data available to select those most worthy of training for higher posts. Even now, no-one pretends that the M.R.C.P. or F.R.C.S. qualifies a man as a medical or surgical consultant. There must be quite independent evidence of talent, stability, industry, and experience before he attains this rank.

The Edinburgh membership is more realistic in so far as, although there is a careful test in general medicine, the candidate must also present himself in a selected subject. In this way he can obtain credit for a wide variety of special knowledge and study a particular field with considerable advantage to himself. Although this system is not recent it fits in far better with the modern scene, particularly as selected subjects are not laid down rigidly and a man may profess anything from hæmodynamics to parasitology and use knowledge and experience obtained while training for and carrying out original work as well as clinical work. I hope to see this aspect of the Edinburgh membership considerably extended.

Conclusion

Thus, in summary, it is my contention that the development of the young doctor in the medical centres is not integrated sufficiently. He has too little clinical work as a student, too much as a houseman, and an odd mixture of all or none as a registrar. There is a lack of team-work and discussion and education which will give a continually expanding interest and experience in both clinical work and research. The non-university areas, on the whole, are only able to meet their clinical commitments, and leave research and clinical and scientific liaison to the departments with university affiliations. With their

present clinical responsibilities and facilities they can do little else.

I have suggested that the teaching hospitals can no longer afford to leave the main effort of modern research and investigation to the university areas and that, as a remedy, the appropriate authorities—notably the Ministry or Department of Health—should give the non-university areas adequate staff and facilities. More of the money being made available for research should reach the main body of clinical medicine in the teaching hospitals all over the country. I have contended that increased junior appointments and facilities are not only desirable to give all young men in teaching hospitals the opportunity to carry out some original investigations, but also necessary on strictly practical terms in order to maintain a high general standard of medical treatment. I have inferred that opportunities for research as well as clinical experience should be equal throughout the teaching hospitals and that these opportunities should be early. I would like to see the unfortunate gap between academicians and non-academicians greatly reduced at all stages of seniority. I have also suggested that all the senior staff of teaching hospitals should be grounded in investigative methods at some time in their career, even though they may be later committed to full-time clinical work.

Let me now deal with possible counter-arguments. Firstly, can the country afford to do this even if it is highly desirable? One must have faith in the future. Increased research leads to increased discovery just as the day follows the night. Increased discovery means the further defeat of disease and the ultimate saving of millions of pounds apart from the relief of human misery and tragedy. Edinburgh has recently seen how modern discoveries combined with great enthusiasm have defeated tuberculosis and how large funds and organisations have been released to attack other less dramatic but disabling respiratory diseases such as bronchitis which cost us vast sums of money each year.

Further, if all young doctors who have been selected to work in the great medical centres have opportunities for research in their early years, then again it is inevitable that their knowledge and understanding of recent developments in medicine will rise abruptly. These young men will in time control future activities and their experience will ensure more efficient and economically planned investigations and treatment.

Again, the students passing through the medical schools must be affected by these activities and develop better professional judgment, particularly concerning therapy and drugs, which will increase the economic efficiency of the whole medical service.

Secondly, is there a danger in too many people attempting to undertake investigative work, and will funds be dissipated and standards lowered? Shall we leave research to the chosen few? Will we breed a generation of half-baked clinicians and half-baked researchers? The younger generation certainly do not believe so. They are anxious to contribute, if even a little, and live a fuller intellectual life in their early professional years than is obtained in many routine clinical tasks. They must be allowed to maintain and even increase their initial enthusiasm. Successful investigators are not easily recognised. Research talent, like gold, is where you find it. It is now generally agreed that above a certain level of intelligence a man can be judged only by his sustained performance in a particular field. This is another important reason why an increased number of young men should be allowed to measure themselves as research-workers at an early stage of their career. Research is an unremitting challenge, and we do not want young men in our medical centres to develop a routine nine-to-five mentality and expect their careers to be laid out like railway time-tables. It is also important to remember that the average intelligent man can also be trained and stimulated to make very useful contributions.

I believe that an increase in research throughout the medical schools will greatly raise the standards among those who are already professional research-workers. Many of us do not like being treated with reverence as authorities on subjects which we have not fully mastered ourselves. More searching and critical inquiry from informed younger men will do us and our research a great deal of good, and not let us rest excessively long on little victories of years ago.

What of the dangers of a falling-off of the standards of clinical care of the patients? I have already pointed out that highly specialised knowledge and techniques are essential to efficient modern clinical medicine. Good clinical medicine cannot stand still. In bygone days important discoveries in biological science did not reach clinical medicine for decades or even centuries. Now they enter and challenge clinical procedure in a few months. We must, however, always remember that our final responsibility is to the patient, and that if new research is to be initiated then there must be an appropriate increase in staff and facilities so that each patient receives the same if not more personal attention. I feel that the danger of reduced clinical efficiency is a very remote one in the Edinburgh medical school with its strong tradition of service and responsibility.

CONVERSION OF GLYCINE TO OXALATE IN PRIMARY HYPEROXALURIA

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PRIMARY hyperoxaluria is characterised by a continuous high urinary oxalate excretion (100–400 mg. per 24 hours) which causes extensive urinary stone formation and nephrocalcinosis. The patients die in childhood or early adult life from renal failure or the effects of hypertension.

Disseminated extrarenal calcium-oxalate deposits (oxalosis) are found at necropsy (Archer, Dormer, Scowen, and Watts 1957a, Scowen, Stansfield, and Watts 1959). The familial incidence of some cases indicates that the disease is genetically determined (Scowen, Watts, and Hall 1959). Previous investigations have suggested that the persistently elevated urinary oxalate excretion does not result from excessive oxalate absorption or from a low renal oxalate threshold (Archer et al. 1958a).

Oxalate can be formed metabolically from glyoxylate which is the intermediate compound on the oxidative pathway of glycine metabolism (Weinhouse and Friedmann 1951, Weinhouse 1955). This suggested that the metabolic lesion in

primary hyperoxaluria might involve excessive formation of oxalate from glycine, either because of a primary failure to metabolise glyoxylate normally or because of excessive glycine metabolism via this pathway. The work of Watts and Crawhall (1959) on certain quantitative aspects of glycine metabolism indicates that such a metabolic lesion need involve only a very small proportion of the total glycine metabolic turnover to produce the increased amounts of oxalate which patients with primary hyperoxaluria excrete. The observation that large doses of sodium benzoate, given to patients with primary hyperoxaluria to produce gross glycine depletion by hippurate formation, were associated with a temporary decrease in the urinary oxalate excretion gave this view some preliminary support (Archer et al. 1958a).

Our present investigation was designed to determine directly whether glycine is the precursor of the urinary oxalate in primary hyperoxaluria, and, if so, the approximate proportion of the urinary oxalate derived from this source. The latter was achieved by measuring the dilution of isotopically labelled carbon (^{13}C) during its incorporation into the urinary oxalate from the glycine of the first glycine metabolic pool (i.e., the pool of glycine with which a dose of glycine mixes immediately after absorption and distribution, and which can be sampled by means of the uncombined urinary glycine [Watts and Crawhall 1959]). A similar study on a normal subject is reported in another paper (Crawhall, de Mowbray, Scowen, and Watts 1959). Some of our results have already been reported preliminarily (Scowen et al. 1958, Watts et al. 1958).

The Study

Four patients were selected for study.

CASE 1 was a girl aged 11 years, height 4 ft. 9 in. (145 cm.), weight 65 lb. (29·6 kg.), with bilateral renal calculi and a reduced urea-clearance. Her blood-urea was normal, there was no arterial hypertension, and her daily urinary oxalate excretion was about 200 mg.

CASE 2 was boy aged $14^3/_4$, height 4 ft. 11 in. (150 cm.), weight 92 lb. (41·9 kg.), with bilateral renal calculi but no evidence of grossly impaired renal function; his daily urinary oxalate excretion was about 300 mg.

CASE 3, a boy aged 5 years, height 3 ft. 5 in. (104 cm.), weight 38 lb. (21·4 kg.), had bilateral renal calculi but no evidence of grossly impaired renal function, and a daily urinary oxalate excretion of about 100 mg.

CASE 4, a girl aged 7 years, height 3 ft. 9 in. (114 cm.), weight 47 lb. (21·4 kg.), had bilateral renal calculi, a reduced urea-clearance, normal blood-urea, and a daily urinary oxalate excretion of about 150 mg. She was the sister of case 3.

All the investigations were performed in hospital. A repetitive diet containing about 40 g. protein was given, from which foods believed to be rich in oxalate (rhubarb, strawberries, chocolate, cocoa, beets, and spinach) were omitted, and copious draughts of water were prescribed to promote diuresis. 6-hour urine collections were made and transferred immediately to plastic bottles which were stored in a deep-freeze cabinet (−20°C). After a preliminary acclimatisation, during which the patient became accustomed to the urine-collection routine, [1-^{13}C]-glycine (2·56 mg. [0·033 millimol] per kg. body-weight, 49·8 atoms % ^{13}C excess) dissolved in distilled water was given by mouth 6-hourly for 4 days. The [1-^{13}C]-glycine was given to coincide with the start of a 6-hour urine-collection period.

Materials and Methods

[1-^{13}C]-glycine (49·8 atoms % ^{13}C excess) was synthesised from Ba $^{13}CO_3$ as described by Watts and Crawhall (1959).

Isolation of calcium oxalate.—The urine collections were divided into portions of about 200 ml. The pH was adjusted to 5·2, and calcium oxalate was precipitated essentially as described for the determination of urinary oxalate (Archer et al. 1957b). The precipitates were separated by centrifugation and dissolved in approximately *N*HCl; the combined solutions were filtered through Watman no. 42 filterpaper, and the filtrate was collected in a 50-ml. centrifuge-tube. The pH of the solution was again adjusted to 5·2, and calcium oxalate was reprecipitated by the addition of 8 ml. 5% (w/v) $CaCl_2$. The precipitate was separated by centrifugation and washed twice with 10 ml. of approximately 0·35 *N*NH_4OH, twice with 10 ml. of an acetate buffer (0·2*M*, pH 4·0), twice with 10 ml. of a saturated aqueous solution of lithium carbonate, and twice with 10 ml. water before being dried to constant weight in vacuo over P_2O_5. The purity of the calcium oxalate isolated from each subject's urine was checked by determining the oxalate content of weighed portions of representative specimens of the material which remained after the isotope measurements had been completed satisfactorily. Several independent analytical procedures were employed ($KMnO_4$ titration in conjunction with ignition to CaO and back-titration with standard NaOH after dissolving the ash in standard HCl, and gravimetric assay as $CaSO_4$ or CaO). In all cases the results of the different methods were in agreement, and indicated that the material was pure calcium oxalate.

Isolation of uncombined urinary glycine.—The supernatant which remained after the initial precipitation of calcium oxalate was concentrated at 37°C in an atmosphere of nitrogen under reduced pressure. After removal of hippuric acid by ethyl-acetate extraction at pH 1, the uncombined urinary glycine was isolated from the concentrate as the 2 : 4-dinitrophenyl (D.N.P.) derivative (Watts and Crawhall 1959).

Isotope determinations.—^{13}C-calcium oxalate was combusted to CO_2 in a Pregl-type combustion-tube, and the CO_2 was collected in an apparatus similar to that described by Bradley et al. (1954) for the preparation of $^{14}CO_2$ samples. A small amount of KH_2PO_4 was added to each sample before combustion, to serve as a "flux" ensuring that all the carbon was converted to CO_2, and none remained as

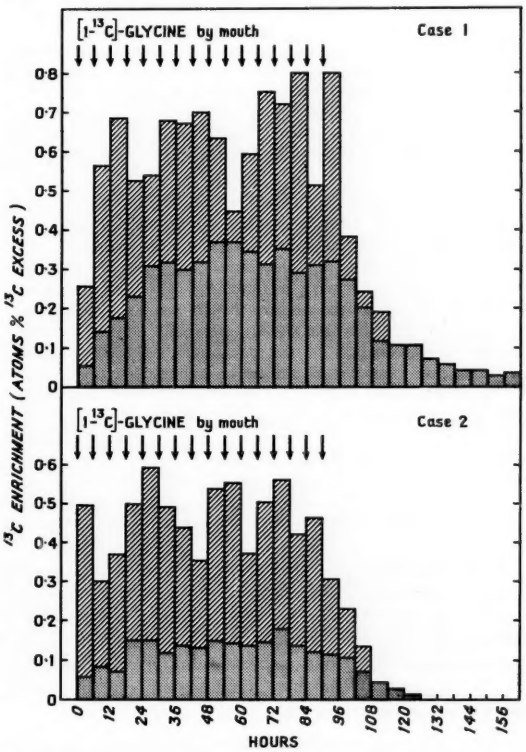

Fig. 1—^{13}C content of the urinary oxalate (represented by the height of the stippled columns) and of the first glycine metabolic pool (represented by the combined heights of the hatched and stippled columns) of cases 1 and 2, who were given [1-^{13}C]-glycine at the times indicated by the arrows.

carbonate. D.N.P.-[1-^{13}C]-glycine was degraded to yield the carboxyl-group carbon atom selectively as CO_2 (Crawhall and Watts 1959). All the determinations were performed at least in duplicate, and the ^{13}C enrichment of the final CO_2 samples was measured on a 'Consolidated Nier Mass Spectrometer' model 21–201, the readings being reproducible within the range $\pm 0{\cdot}003$ atoms % ^{13}C excess. When $^{13}CO_2$ was derived from ^{13}C-calcium oxalate, allowance had to be made for the fact that only one of the two carbon atoms was enriched with ^{13}C. In the case of $^{13}CO_2$ derived from D.N.P.-[1-^{13}C]-glycine a correction factor (1·06) was introduced to allow for a small amount of unenriched CO_2 derived from side reactions in the reagents (Crawhall and Watts 1959).

Results

Measurable amounts of ^{13}C were present in the urinary oxalate excreted during the first 6 hours of [1-^{13}C]-glycine administration. The ^{13}C enrichment in the oxalate increased during the next 12–18 hours, after which it remained relatively constant until the [1-^{13}C]-glycine was stopped (figs. 1 and 2). The time course of the appearance

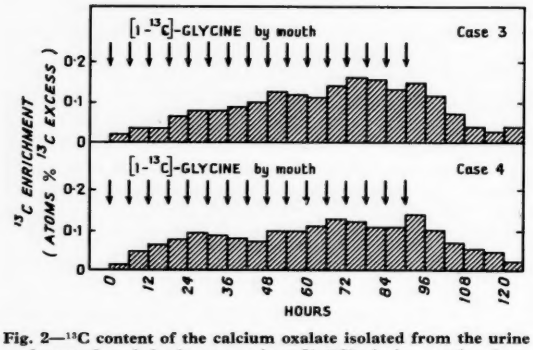

Fig. 2—^{13}C content of the calcium oxalate isolated from the urine of cases 3 and 4 who were given [1-^{13}C]-glycine at the times indicated by the arrows.

of ^{13}C in the urinary oxalate was similar in each of the patients studied, although the absolute values were different.

The isotope content of the first glycine metabolic pool (sampled by means of the uncombined urinary glycine) rose more steeply, attained a higher plateau value during [1-^{13}C]-glycine administration, and decreased more quickly than the ^{13}C-content of the urinary oxalate (fig. 1). The maximum isotope enrichment in the urinary oxalate was always less than the enrichment in the first glycine metabolic pool. In case 1, the mean ^{13}C contents of the oxalate and the first glycine metabolic pool between 24 and 96 hours after starting to give [1-^{13}C]-glycine were 0·327 (S.D. 0·025) atoms % ^{13}C excess and 0·654 (S.D. 0·113) atoms % ^{13}C excess respectively. The isotope enrichment of the urinary oxalate reached a plateau value after only 18 hours in case 2, and the mean ^{13}C enrichments of the oxalate and the first glycine metabolic pool between 18 and 96 hours after starting to give [1-^{13}C]-glycine were 0·146 (S.D. 0·017) atoms % ^{13}C excess and 0·466 (S.D. 0·094) atoms % ^{13}C excess.

These values indicate that about 50% and 32% of the urinary oxalate was derived from the glycine of the first glycine metabolic pool in cases 1 and 2 respectively. Cases 3 and 4 showed a similar pattern of isotope incorporation into the urinary oxalate, and, in view of this, the ^{13}C content of the first glycine metabolic pool was not studied in these patients.

Discussion

Precursor-product relations may be investigated (*a*) by giving a single dose of labelled material and comparing the time course of the appearance and disappearance of the isotopic label in the suspected precursor with that in the suspected product (Zilversmit et al. 1943), or (*b*) by giving the labelled material repeatedly until the metabolic pool of the suspected precursor is maximally labelled with the isotope and then comparing the isotope contents of the suspected precursor and product during and after the administration of labelled material. The latter procedure is especially valuable when the rate of isotope incorporation into the product is likely to be slow by comparison with the rate of removal of the isotopic label from the precursor pool by alternative metabolic pathways.

Such experiments should be designed so that the amount of the suspected precursor given is small by comparison with the size of metabolic pool with which it will mix; it should be administered in such a way that it mixes rapidly in the pool and the concentration of isotope in the pool remains high during the test period. Watts and Crawhall (1959) showed that these criteria could be fulfilled in experiments designed to study some aspects of the fate of the carbon skeleton of glycine in man after it had entered the first glycine metabolic pool, and they discussed the validity of using the uncombined urinary glycine as a sample of this metabolic pool. ^{13}C-tracer experiments cannot be designed to investigate the reaction glyoxylate $\longrightarrow$ oxalate alone because of the very small amounts of glyoxylate which apparently exist in the body. Measurable amounts of this acid have not been detected in the body-fluids, and it may well only exist as part of an enzyme-substrate complex.

Our present findings indicate that at least the carboxyl carbon atom of glycine is incorporated into the urinary oxalate. The high level of isotope enrichment observed in the urinary oxalate shows that this incorporation is not the result of a series of metabolic transformations involving extensive dilution of the isotope, and suggests that it is not directly linked with any of the major energy-yielding metabolic processes whose intermediary metabolites have high turnover-rates which cause extensive dilution of the labelled carbon atoms of compounds with which they are in equilibrium. In these circumstances it seems very probable that the carbon skeleton of glycine is incorporated into oxalate as a single unit via glyoxylate. This conclusion is compatible with the results of studies on isolated tissues and in animals (see, for example, Trampetti and Vantaggi-Cozzari 1948, Weinhouse 1955, Nakada and Sund 1958). The incorporation of the carboxyl carbon atom of glycine into a normal subject's urinary oxalate (see Crawhall et al. 1959) indicates that a similar metabolic relation exists normally in man, and that the metabolic defect in primary hyperoxaluria does not bring about a chemical transformation which has no counterpart in normal human biochemistry.

Previous evidence for the oxidative metabolism of glycine:

$$\text{Glycine} \rightleftarrows \text{Glyoxylate} \longrightarrow \text{Formate} + CO_2$$
$$\downarrow$$
$$\text{Oxalate}$$

has been derived from in-vitro studies, and the importance of these reactions in the intact animal has been questioned (Arnstein 1954). Our findings are compatible with the operation of at least the first stage of this metabolic pathway, but they do not indicate its quantitative importance relative to the other pathways of glycine metabolism.

The difference between the ^{13}C enrichments in the first glycine metabolic pool and the urinary oxalate in the patients with primary hyperoxaluria could have been due

wholly or partly to exchange of oxalate molecules between the ^{13}C-labelled oxalate in the urine and the unenriched oxalate of the renal calculi present in both cases. But the fact that the ^{13}C enrichments of the urinary oxalate showed no tendency to rise after the first three or four doses of [1-^{13}C]-glycine, and that there was isotope dilution of the same degree in a normal subject as judged by the ratios:

$$\left\{ \frac{\text{mean plateau enrichment of urinary } ^{13}\text{C-oxalate}}{\text{mean plateau enrichment of free urinary } ^{13}\text{C-glycine}} \right\}$$

which were 0·5, 0·314, and 0·408 for cases 1 and 2 and a normal subject (Crawhall et al. 1959) respectively, suggests that exchange was not important in producing this difference and that some of the urinary oxalate is derived from sources other than glycine, such as ascorbate (Curtin and King 1955, Hellman and Burns 1958) or glycollic aldehyde (Friedmann et al. 1956). Glyoxylate is concerned in metabolic reactions which are closely related to the tricarboxylic-acid cycle in some micro-organisms (Campbell et al. 1953, Saz and Hillary 1956, Calleley et al. 1957, Kornberg and Krebs 1957, Kornberg and Madsen 1958). But there is no evidence that these reactions occur in animals, and if they were important in man more isotope dilution would probaby have taken place in our experiments than we observed. Our findings are compatible with the view that the carbon skeleton of about $^1/_3$ to $^1/_2$ of the urinary oxalate is derived from glycine.

The situation we have encountered in primary hyperoxaluria—namely, a high urinary oxalate excretion with about the same degree of isotope dilution between the precursor glycine and the urinary oxalate in the patients and in a normal subject—indicates that about the same proportion of the urinary oxalate is derived from glycine in the patients as in the normal subject. This in turn suggests that the fundamental lesion may be failure to degrade glyoxylate rather than excessive metabolism of glycine via glyoxylate, which would be expected to produce a high urinary oxalate excretion with a greater isotope incorporation in the patients than in the normal subject. The number of subjects studied is small, but our findings have received a measure of independent confirmation from the work of Wyngaarden and Verner (1958) and Wyngaarden (1959), who gave a single oral dose of [1-^{14}C]-glycine to a patient with primary hyperoxaluria and to a normal subject and found ^{14}C in the urinary oxalate during the next 48 hours.

We would stress that only a very small proportion of the total glycine metabolic turnover results in the production of urinary oxalate (Watts and Crawhall 1959), and that it is an error of this minor metabolic pathway involving only about a 5-fold increase in the total oxalate excretion which results in the gross clinical and pathological manifestations of primary hyperoxaluria.

Nakada and Sund (1958) obtained from rat-liver mitochondria a partly purified enzyme which catalyses the oxidative decarboxylation of glyoxylate. Our evidence for the fundamental lesion in primary hyperoxaluria being a failure to degrade glyoxylate in this way could indicate a congenital defect of such an enzyme system. A congenital deficiency would be compatible with our demonstration that the disease is genetically determined (Archer et al. 1958b, Scowen et al. 1959) and with the view that single genes are responsible for single biochemical processes (see, for example, Harris 1953).

Summary

[1-^{13}C]-glycine was given by mouth (2·56 mg. [0·033 millimol] per kg. body-weight, 49·8 atoms % ^{13}C excess, 6-hourly for 4 days) to four patients, including two siblings, with primary hyperoxaluria; the oxalate was isolated from successive 6-hour urine collections and its ^{13}C content was measured. In two cases the ^{13}C content of the first glycine metabolic pool was determined by measuring the ^{13}C enrichment of the uncombined glycine which was isolated as the 2 : 4-dinitrophenyl derivative from each 6-hour urine collection.

The oxalate which was isolated from the first urine collection contained ^{13}C; the amount increased over the first 18–24 hours of [1-^{13}C]-glycine administration, and it then remained fairly constant. The isotope content of the first glycine metabolic pool rose more steeply and attained a higher plateau value during [1-^{13}C]-glycine administration and decreased more quickly than the ^{13}C content of the urinary oxalate when administration of the labelled aminoacid was discontinued.

Thus in these patients the carbon skeleton of about $^1/_3$ to $^1/_2$ of the urinary oxalate was derived from the carbon skeleton of glycine, probably via glyoxylate.

The results are compatible with the view that primary hyperoxaluria arises from an inborn metabolic error involving a failure to degrade glyoxylate normally, and that an abnormal conversion of glyoxylate to oxalate is secondary to this error.

We are pleased to acknowledge financial support from the governors of St. Bartholomew's Hospital which enabled us to purchase the large amount of ^{13}C needed for this work. The investigations on cases 2–4 were made possible only by the unstinted cooperation of Dr. E. G. Hall and his colleagues at the Alder Hey Children's Hospital, Liverpool. Prof. A. Wormall, F.R.S., generously placed the mass spectrometer in the Department of Biochemistry at St. Bartholomew's Hospital Medical College at our disposal. We are indebted to Dr. H. E. Archer for checking the purity of some of our calcium-oxalate samples, and to Miss E. D. Bell and Mr. L. Rawlings for their skilled assistance.

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CONVERSION OF GLYCINE TO OXALATE IN A NORMAL SUBJECT

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THIS investigation was undertaken to determine whether the feeding of isotopically labelled [1-^{13}C]-glycine to a normal subject results in a pattern of isotopic labelling of the urinary oxalate similar to that observed in cases of primary hyperoxaluria (Crawhall, Scowen, and Watts 1959).

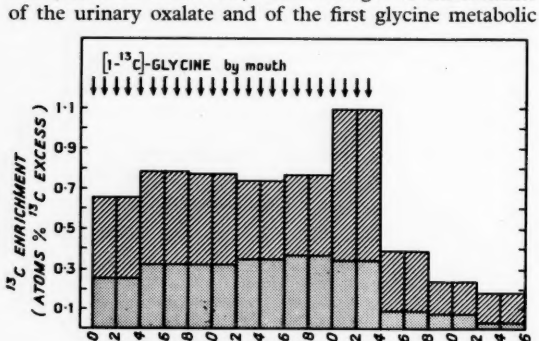
The Study

The subject was a healthy man, aged 38, weight 202 lb. (91 kg.), height 6 ft. 3$^1/_2$ in. (192 cm.), whose average urinary oxalate excretion was about 20 mg. per 24 hours. He took a repetitive 50 g.-protein diet for 12 successive days, and 24-hour urine collections were made throughout. [1-^{13}C]-glycine (2·56 mg. [0·033 millimol] per kg. body-weight, 49·8 atoms % ^{13}C excess) dissolved in water was given 6-hourly from the 4th to the 9th days inclusive of the investigation. The oxalate and the uncombined urinary glycine (a sample of the first glycine metabolic pool [Watts and Crawhall 1959]) were isolated from the 24-hour urine collections, made during and after [1-^{13}C]-glycine administration, and their ^{13}C contents were determined as described previously (Crawhall et al. 1959, Watts and Crawhall 1959).

24-hour urine collections were used in the present investigation instead of 6-hour collections, because 5–6 mg. of calcium oxalate is needed for each ^{13}C determination, and preliminary experiments showed that a full 24-hour collection of the subject's urine yielded only about 20 mg. of pure calcium oxalate.

Results

The ^{13}C contents of the urinary oxalate and of the first glycine metabolic pool are shown in the figure. That of the first glycine metabolic pool fluctuated more widely than the oxalate enrichment when [1-^{13}C]-glycine was given, and the pool retained a measurable isotope enrichment for a longer period after administration ceased than in the investigation on patients with primary hyperoxaluria (Crawhall et al. 1959). The average ^{13}C enrichments of the urinary oxalate and of the first glycine metabolic pool whilst [1-^{13}C]-glycine was being given were 0·328 (S.D. 0·042) atoms % ^{13}C excess and 0·803 (S.D. 0·138) atoms % ^{13}C excess respectively. The isotope was therefore diluted about 2$^1/_2$ times during the conversion of glycine from the first glycine metabolic pool to oxalate, indicating that about 40% of the urinary oxalate was derived from glycine during this period.



^{13}C content of the urinary oxalate (represented by the height of the stippled columns) and of the first glycine metabolic pool (represented by the combined heights of the hatched and stippled columns) of a normal subject given [1-^{13}C]-glycine at the times indicated by the arrows.

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THE USE OF AMYL NITRITE IN THE DIAGNOSIS OF SYSTOLIC MURMURS

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ACCURATE interpretation of systolic murmurs is always important but often difficult. They may be divided into ejection and regurgitant murmurs (Leatham 1952). Ejection systolic murmurs are crescendo-diminuendo in shape, commencing after the first heart-sound and ending before the second sound. They are caused by turbulent ejection of blood from the left or right ventricle into the aorta or pulmonary artery when there is valve abnormality (with or without stenosis), or simply by increased flow through a normal valve. Regurgitant murmurs are pansystolic, extending from the first to the second sound and often slightly beyond. The loudness may vary little throughout systole or there may be a late systolic crescendo. They result from regurgitation of blood through incompetent mitral or tricuspid valves, or from a left-to-right shunt through a ventricular septal defect or a patent ductic ateriosus. The murmurs are pansystolic because flow is from a high to a low pressure region, commencing during the isometric contraction phase and continuing into the relaxation phase after aortic-valve closure.

Right or left sided ejection and regurgitant murmurs are usually distinguished by their site of maximal intensity, conduction, character of the heart-sounds, effect of inspiration, and collateral evidence. At times, however, accurate diagnosis may require phonocardiography, and the use of certain well-established manœuvres to differentiate murmurs—such as exercise, the effect of deep inspiration, pressor agents, and the Valsalva manœuvre. Even with these aids the diagnosis may remain uncertain; it may, for example, be impossible to differentiate the murmurs of pulmonary stenosis, Fallot's tetralogy, ventricular septal defects, and mitral and tricuspid valve incompetence.

We have reported elsewhere the opposite effect of amyl nitrite on the systolic murmur of pulmonary stenosis and Fallot's tetralogy (Vogelpoel et al. 1958, 1959).

Inhaled amyl nitrite caused sudden systemic vasodilatation resulting in pronounced fall of blood-pressure and tachycardia, followed by a greatly increased venous return to the right heart. In pulmonary stenosis with intact ventricular septum the increased venous return produced a sudden and marked rise in right centricular pressure which persisted long after the systemic pressure had returned to normal. The increased flow through the stenosis caused a striking intensification of the systolic murmur, which accurately reflected the rise in the right ventricular systolic pressure shown by synchronously recorded pressure and sound tracings. The maximum loudness and pressure usually occurred after about 45 seconds, and thereafter subsided and returned to resting level after about 3 minutes.

In Fallot's tetralogy the increased venous return induced by amyl nitrite did not cause a rise in right ventricular pressure. The pressure, in fact, fell because the presence of a large ventricular septal defect acted as an efficient escape route for the overfilled right ventricle, resulting in a fall of the right ventricular systolic pressure with the drop in systemic blood-pressure. It is well established that the right ventricular pressure in the tetralogy is determined not by the higher pulmonary stenotic resistance but by the systemic resistance; hence sudden reduction of the latter by amyl nitrite decreased pulmonary blood-flow and increased the right-to-left shunt. This was reflected clinically by an easily detected shortening and softening of the murmur, and increase in cyanosis during the peak action of amyl nitrite.

The behaviour of the systolic murmur after amyl nitrite was so different in the two conditions that the diagnosis could be established by this means at the bedside. The great merit of the test was the accuracy with which it distinguished mild or acyanotic Fallot's tetralogy from moderately severe pulmonary or infundibular stenosis with intact ventricular septum. These conditions may present indistinguishable clinical, phonocardiographic, electrocardiographic, radiological, and catheter findings, and correct diagnosis is imperative in planning the surgical procedure.

Because the test proved so helpful, simple, and harmless, and since these observations demonstrated the ability of amyl nitrite to affect the circulation—an initial drop in systemic blood-pressure followed by increased filling of the right heart and increased forward flow—the response of other murmurs was observed. We report here the effect of amyl-nitrite inhalation on systolic murmurs of various causes and its use in diagnosis.

Material and Methods

181 cases were selected for clinical and phonocardiographic study, in whom the diagnosis had been firmly established, either by cardiac catheterisation (right-sided lesions), surgery, or by usually accepted clinical, electrocardiographic (E.C.G.), and radiological criteria. Of the left-sided regurgitant murmurs there were 10 cases of mitral regurgitation, 30 of ventricular septal defect with left-to-right shunt (proven by cardiac catheterisation), 8 of patent ductus arteriosus, 3 with bronchopulmonary collateral circulation, and 1 case of a traumatic ateriovenous fistula in the neck. Of the right-sided regurgitant murmurs, there were 10 cases of tricuspid incompetence. Of the aortic ejection systolic murmurs 15 cases had aortic stenosis, 5 had aortic systolic murmurs associated with dominant aortic incompetence, and 5 had coarctation of aorta. Of the pulmonary ejection systolic murmurs 15 were due to increased flow from atrial septal defect without stenosis (proven by catheterisation), 2 were due to idiopathic dilatation of the pulmonary artery (catheter proof); while the effect of pulmonary stenosis was reported in a separate study on 22 cases of tetralogy, 12 of pulmonary valvular stenosis, and 3 of infundibular stenosis (Vogelpoel et al. 1959), to which series 5, 8, and 2 cases respectively have since been added. There were 25 cases with innocent systolic murmurs, but since precise anatomical diagnosis was not possible they were analysed separately.

High-frequency phonocardiograms (P.C.G.) were recorded in all cases using the 'N.E.P.' multichannel apparatus. A control P.C.G. was taken with one microphone at the site of maximal intensity of the murmur and another at a suitable site (usually fourth left interspace or mitral area), to record the aortic second sound, together with an E.C.G. The patient was then encouraged to take deep inhalations of amyl nitrite from a broken ampoule held close to the nose for about 30 seconds. The desired brisk fall in blood-pressure, together with flushing, and tachycardia were usually produced by 10 deep inhalations. P.C.G.'s at the *same attenuations* were recorded continuously during and after the inhalation, and frequent tracings at fast paper-speed (80 mm. per sec.) were made during *held expiration* throughout the study. Between the fast strips the recordings were made at slow paper-speed (2·5 mm. per sec.). The duration of the inhalation was noted and a signal was registered at 7·5-second intervals after withdrawal of the ampoule. Blood-pressure readings (cuff method) were taken at very frequent intervals by one of us, while another observed the changes in the murmur through the audiophone. Recordings were continued until the murmur intensity had returned to normal; in the case of stenotic ejection murmurs this required 3–4 minutes, whereas a shorter time was needed for the regurgitant murmurs. The procedure was usually repeated at least once.

During cardiac catheterisation in 25 cases of ventricular septal defect and 4 with patent ductus we studied the effects of amyl nitrite on the systemic and right ventricular or pulmonary arterial pressures with synchronously recorded P.C.Gs, using a technique similar to that described in a previous study on pulmonary stenosis and Fallot's tetralogy (Vogelpoel et al. 1958, 1959). The response of the brachial and left ventricular pressures and murmur was similarly studied in 3 cases of severe aortic stenosis subjected to diagnostic left ventricular puncture. By these methods the change in the murmur could be precisely correlated with the change in the relevant pressure gradient (figs. 1, 2, and 5).

Technique of using Amyl Nitrite as a Bedside Test

The dose of amyl nitrite must be sufficient to induce maximal hypotension, and continuous auscultation must be maintained before, during, and after inhalation in order to appreciate the softening of left-sided regurgitant murmurs. Having carefully noted the intensity and duration of the murmur, auscultation is continued at the selected site while the patient is encouraged to inhale the vapour deeply for some 20–30 seconds. Marked tachycardia and flush signal the end-point, whereupon the crushed ampoule is withdrawn. Hypotension and considerable tachycardia usually persist 20–30 seconds thereafter, during which period left-sided regurgitant murmurs and the murmur of Fallot's tetralogy soften. After 30–45 seconds the tachycardia rapidly diminishes and the blood-pressure rises. During this phase left-sided regurgitant murmurs rapidly recover, while ejection murmurs reach their peak intensity. After 1 minute the flush vanishes, pulse-rate and blood-pressure are usually restored, but ejection murmurs due to stenosis continue to remain loud for 2 or more minutes.

In children anxiety, crying, and struggling may interfere with the test. Simple explanation of its purpose and the transitory nature of the effects will usually obtain cooperation. A rehearsal with instructions to ensure proper deep breathing while holding an uncrushed ampoule under the nose often helps. Since ampoules often break with a loud noise, they should be crushed well away from the patient, before being held close to the nose. In infants a much smaller dose is required and diagnostic changes are usually observed before the patient cries or struggles.

The odour of amyl nitrite is its only drawback, but this may be greatly minimised by prompt disposal of the broken ampoule into a bottle containing a deodorant solution. An alcoholic solution of caustic soda was found satisfactory for this purpose. It was prepared by first dissolving 40 g. of

NaOH in 100 ml. of water and then adding absolute alcohol to 1 litre.

Results

On inhaling amyl nitrite most patients developed a considerable flush, tachycardia, and a rapid fall in blood-pressure. The aortic second sound always became softer because of hypotension, and the first sound much louder because of tachycardia, while a summation gallop frequently developed. As the effects wore off, the flush disappeared, the tachycardia gradually subsided, and blood-pressure gradually returned to normal, sometimes followed by a temporary overshoot. The effect on the systolic murmur differed according to the condition present, and the increase or decrease in intensity was usually easy to hear.

Left-sided Regurgitant Systolic Murmurs

Left-sided regurgitant systolic murmurs became shorter and softer, the decrease in intensity being much more pronounced in the latter half of systole. The change in the murmur was maximal during and shortly after the inhalation (first 10–20 seconds); thereafter with the gradual return to normal of the blood-pressure the murmur slowly returned to its former length and loudness after about 45 seconds, sometimes becoming a little louder for a short time if there was an overshoot in blood-pressure.

Ventricular septal defects.—In small defects (12 cases with normal right ventricular pressures and small left-to-right shunts [0·5–4·8 litres per min.]) the softening and shortening of the murmur were shown to be due to the pronounced drop in pressure gradient between the left and right ventricle (fig. 1). The average reduction in systemic pressure was 46/29 mm. Hg, while the right ventricular pressure either remained unchanged, dropped, or increased slightly. In all cases the systemic pressure, which fell rapidly and progressively throughout the inhalation, remained much reduced for some 30 seconds after withdrawal of the ampoule and thereafter progressively increased (fig. 1). The greater the hypotension produced, the greater the change in the murmur. If the dosage was inadequate or the cooperation of the patient was poor, the hypotensive response was less and the effect on the murmur was correspondingly less impressive.

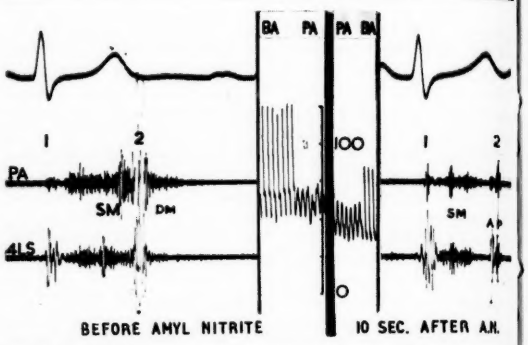

Fig. 2—Patent ductus arteriosus with moderate pulmonary hypertension. (Systemic flow 5·04 litres per min.; pulmonary flow 8·34 litres per min.; pulmonary vascular resistance 5·8 units.)

The immediately consecutive brachial (BA) and pulmonary arterial (PA) pressure tracings showed a wide gradient in systole but none in end-diastole, though possibly trivial in early diastole. This accounted for the loud pansystolic murmur continuing into a very short diastolic murmur in the pulmonary area (PA). 10 sec. after amyl nitrite the diastolic murmur disappeared, while the systolic murmur became much softer and shorter, owing to the abolition of diastolic gradient in early diastole and marked reduction in systolic gradient. The BAP fell from 125/52 to 85/35 and PAP from 70/53 to 60/38 mm. Hg.

In large ventricular septal defects with considerable left-to-right shunt, low pulmonary vascular resistance, and equalisation or near equalisation of left and right ventricular pressures (hyperkinetic pulmonary hypertension), the response to amyl nitrite was less consistent. There were 5 such cases in whom the murmur either softened slightly or not at all. In a case with 3 defects (shown at operation), giving a large left-to-right shunt of 9 litres per min. and mild pulmonary hypertension, the murmur softened markedly with amyl nitrite. The

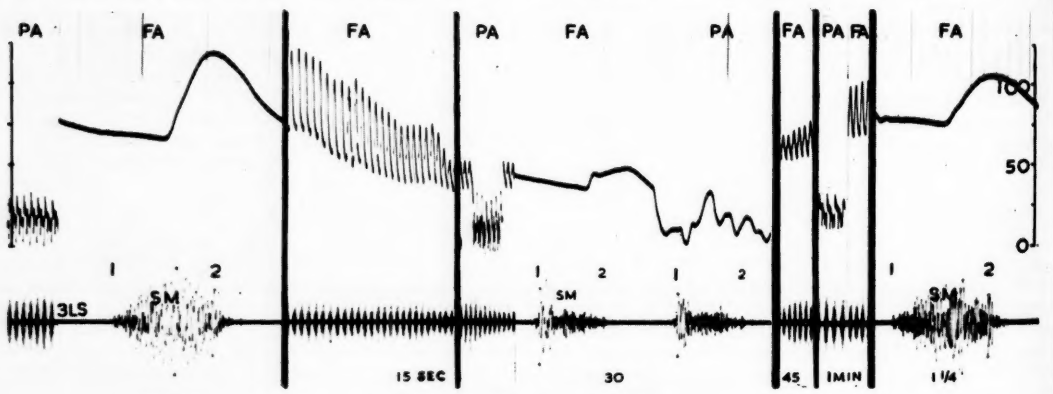

Fig. 1—Ventricular septal defect with small left-to-right shunt (1 litre per min.). Effect of amyl nitrite on immediately consecutive pulmonary (PA) and femoral arterial (FA) pressures and synchronously recorded phonocardiograms.

Before inhalation the loud pansystolic murmur (SM) had a mid-systolic crescendo and extended beyond the aortic second sound (2), simulating a pulmonary stenotic murmur. The long murmur was caused by a marked systolic gradient (90 mm. Hg) between left and right ventricle, assuming that FA (120/72 mm. Hg) and left ventricular (LV) systolic pressures were equal, and that PA (30/5 mm. Hg) and right ventricular (RV) systolic pressures were equal (pulmonary stenosis was excluded). Cardiac rate was 80 per min. During the 15 seconds' inhalation, FAP fell rapidly to 55/35 mm. Hg, and after 30 sec. the marked softening and moderate shortening of the murmur was attributed to the great reduction of the LV–RV systolic gradient to 15 mm. Hg (FAP 50/38; PAP 35/2 mm. Hg). Tachycardia (130 per min.) and very low FA diastolic pressure accounted for loud first and very soft second sound respectively. FAP began to rise after 45 sec., PAP remaining virtually unchanged (32/10 mm. Hg); by 1 min., the LV–RV systolic gradient (75 mm. Hg) was rapidly increasing and by $1^1/_4$ min. the murmur and heart-rate have virtually returned to the initial level. (Recordings in this and subsequent studies have been made at 2·5 mm. per sec. and 75 mm. per sec., and the phonocardiograms were always recorded during held expiration at the same attenuation. Each vertical line measures 0·04 sec.)

presence of pulmonary or infundibular stenosis in addition to the septal defect made the response of the murmur to amyl nitrite less predictable (vide infra).

Patent ductus arteriosus.—A marked reduction of the aorticopulmonary systolic and diastolic gradient accounted for the disappearance of the diastolic component and marked shortening of the systolic murmur in 4 cases who were catheterised. In one of these the shunt was large with moderate pulmonary hypertension; the systolic pressures between aorta and pulmonary artery being widely discrepant (60 mm. Hg), but the diastolic pressures were equal. A pansystolic murmur was present in the pulmonary area with a difficult diastolic murmur. Amyl nitrite reduced the aortic pressure from 130/55 to 80/35 and the pulmonary arterial pressure from 70/52 to 60/40 mm. Hg 10 seconds after the inhalation, accounting for the great shortening and softening of the systolic murmur and disappearance of the diastolic component (fig. 2). In 4 other cases not catheterised the disappearance of the diastolic murmur and shortening of the systolic component followed the fall in systolic blood pressure (cuff method), suggesting a comparable mechanism. Similar observations were made in 3 patients with continuous murmurs due to bronchopulmonary collateral

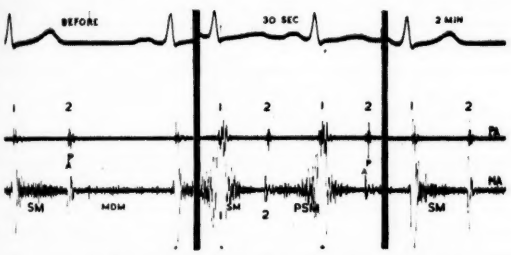

Fig. 3—Mitral incompetence with minimal stenosis.

Before amyl nitrite the pansytolic murmur at the mitral area (MA) was associated with a soft mid-diastolic murmur (MDM) but no presystolic murmur. 30 sec. after the inhalation the systolic murmur became much shorter and softer, presumably due to reduced left ventricular-left atrial gradient since the systolic blood-pressure had fallen from 125 to 90 mm. Hg. A loud presystolic murmur (PSM) emerged and the mid-diastolic murmur became louder due to increased forward flow across the mitral valve, since the cardiac rate increased from 70 to 118 per min. The tachycardia intensified the first sound while the fall in systemic pressure softened the aortic component (A). The slight splitting of the second sound (A, P) might be due to relative shortening of left ventricular (LVP) systole or prolongation of right ventricular (RV) systole, or both. After 2 min. the presystolic murmur had disappeared, and the mid-diastolic murmur and heart-sounds had returned to initial levels, while the systolic murmur was becoming more prolonged with the increasing LV–LA gradient, because of the rising systolic blood-pressure (120 mm. Hg).

circulation and in 1 patient with a traumatic subclavian arteriovenous fistula.

Mitral incompetence.—The left ventricular-left atrial systolic gradient was assumed to have been reduced, causing the murmur to soften and shorten, since the change in the murmur was related to the drop in systolic blood-pressure in all cases (fig. 3).

Right-sided Regurgitant Murmurs (Tricuspid Incompetence)

There was usually a considerable increase in loudness and length, presumably owing to increased venous return to the right heart (fig. 4). In functional tricuspid incompetence associated with gross heart-failure, however, little change occurred.

Left and Right Sided Ejection Murmurs

With the important exception of Fallot's tetralogy, ejection murmurs became louder, though the degree of intensification varied. The maximal increase was usually reached later after amyl nitrite than the maximal decrease of left-sided regurgitant murmurs.

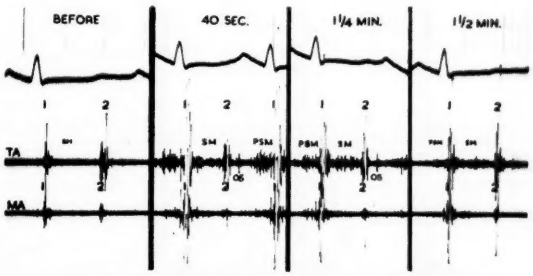

Fig. 4—Mild tricuspid incompetence and stenosis.

Before amyl nitrite there was a very soft systolic murmur in the tricuspid area (TA), brought out by deep inspiration (not shown). 40 sec. after inhalation loud pansystolic and presystolic murmurs developed together with a tricuspid opening snap (OS). The cardiac rate increased from 90 to 130 per sec. causing a greatly intensified first sound. The pulmonary second sound greatly increased while the aortic component diminished. The systolic blood-pressure fell from 115 to 85 mm. Hg and clearly had no direct influence on the murmurs. These findings were unchanged even after $1^1/_4$ min., although cardiac rate was now 120 and systolic blood-pressure 90 mm. Hg. At $1^1/_2$ min. the murmurs began to subside and opening snap to disappear (rate 100 per min., systolic blood-pressure 100 mm. Hg).

The increase in loudness was much greater and more sustained when the murmur resulted from organic *stenosis* than from increased flow through non-stenosed valves, provided that cardiac failure was not present or imminent. It was more striking in pulmonary than in aortic stenosis. In pulmonary and aortic stenosis the peak loudness often occurred 40–60 seconds after the inhalation, and at times took as long as 3 minutes to return to resting level (fig. 5). In ejection murmurs not due to stenosis—such as atrial septal defect, idiopathic dilatation of the pulmonary artery, and in to-and-fro aortic murmurs of pure aortic incompetence—the increased loudness of the systolic murmur was seldom great and simply paralleled the increased cardiac rate, returning quickly to resting level after about 45 seconds.

In 15 cases of pure pulmonary stenosis of varying severity, increased stroke flow and murmur was always associated with a marked and prolonged rise in right ventricular pressure (Vogelpoel et al. 1959) (fig. 5), whereas in all 6 cases of atrial septal defect the increased venous return was ejected without

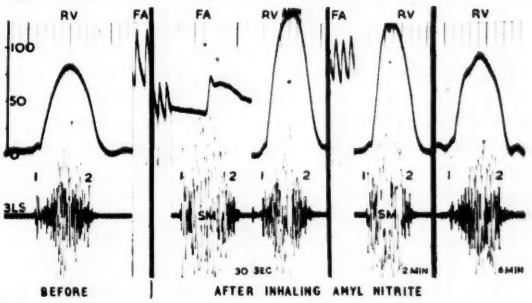

Fig. 5—Moderately severe infundibular stenosis with intact ventricular septum.

Before amyl nitrite the loud pansystolic murmur, maximal in the third left intercostal space (3LS), had a midsystolic crescendo and extended beyond the aortic second sound (2), similar to SM in fig. 1. Pulmonary component was unrecordable. Right ventricular pressure (RV) and femoral arterial pressure (FA) were 85/5 and 115/65 mm. Hg respectively. Cardiac rate was 110 per min. 30 seconds after inhalation the marked fall in systemic pressure to 65/35 was associated with a marked rise in RVP to 135/7 mm. Hg, proving that the ventricular septum was intact and accounting for the greatly intensified murmur. Cardiac rate 150 per min. After 2 min., although FAP had returned to initial level, RVP (120/7 mm. Hg) and murmur were still much increased, and even after 6 min. RVP (92/10 mm. Hg) and murmur length had not quite returned to resting level.

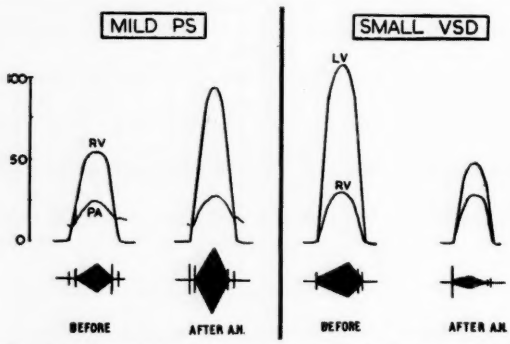

Fig. 6—Differentiation of pulmonary stenosis from ventricular septal defect (V.S.D.).

Before amyl nitrite the systolic murmur of mild or moderate pulmonary stenosis may simulate that of V.S.D. with left-to-right shunt. However, amyl nitrite intensifies the former by increasing right ventricular-pulmonary arterial gradient, and softens the latter by reducing the left ventricular-right ventricular systolic gradient.

significant rise in right ventricular pressure, and hence with less pressure velocity and turbulence. This appeared to account for the greater and more prolonged intensification of the murmur when the valve was stenosed. A similar mechanism was assumed for the more prolonged change in stenotic as opposed to non-stenotic aortic ejection murmurs, although none of the mild cases were subjected to left-heart catheterisation. In aortic stenosis the relative lateness and prolonged intensification of the murmur is probably due to delay in transmission of the increased venous return from the right to left heart via the pulmonary circulation.

Combined Lesions

The presence of combined lesions modified the response to amyl nitrite. For example, where pulmonary stenosis and ventricular septal defect occurred together the response depended on the severity and the size of the defects relative to each other. In Fallot's tetralogy, where the stenosis is severe, the presence of a large septal defect resulted in softening and shortening of the pulmonary ejection murmur in all 27 cases studied, enabling differentiation from pulmonary stenosis with intact ventricular septum to be achieved (fig. 7). When milder degrees of stenosis were combined with septal defects of varying sizes, a fusion of ejection and regurgitant murmurs resulted and the response to amyl nitrite was less predictable. Of 11 such cases, the murmur softened in 7, failed to change in 2, and in 2 initial softening was followed by moderate intensification. The mechanism will be discussed elsewhere.

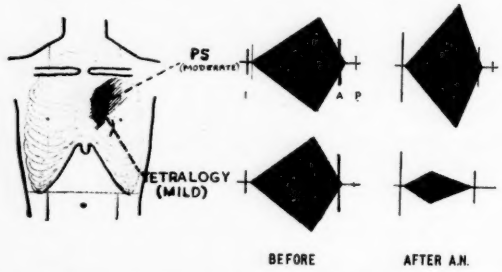

Fig. 7—Pulmonary stenosis: is the ventricular septum intact or not?

Before amyl nitrite the murmur and width of splitting of the second sound in pulmonary valvular or infundibular stenosis with intact ventricular septum may be indistinguishable from mild Fallot's tetralogy. Amyl nitrite intensifies the former with persistence of the soft pulmonary component, while it softens and shortens the latter with transient disappearance of the pulmonary component if present.

Amyl nitrite induced changes in diastolic murmurs which were helpful in the diagnosis of the systolic murmur. Thus, in mitral or tricuspid regurgitation due to organic valve disease, the increased forward flow across the valves greatly increased mid-diastolic and presystolic murmurs, sometimes eliciting them when undetected at rest (figs. 3 and 4). In atrial septal defect the tricuspid mid-diastolic flow murmur was always greatly augmented and was sometimes brought out when deep inspiration had failed. Aortic diastolic murmurs always became softer or temporarily disappeared, while pulmonary incompetent murmurs usually remained unchanged or became louder.

Effect of Cardiac Failure

The effect of amyl nitrite was much less striking or absent in pulmonary or aortic stenosis when cardiac failure was present or imminent.

Thus, in two cases of severe pulmonary stenosis in cardiac failure there was no appreciable increase in loudness, and in one a delayed rise of only 40 mm. Hg in right ventricular systolic pressure was induced. Similarly in 3 cases of severe aortic stenosis the systolic gradient between the left ventricle and brachial artery increased by 55, 21, and 15 mm. Hg. This

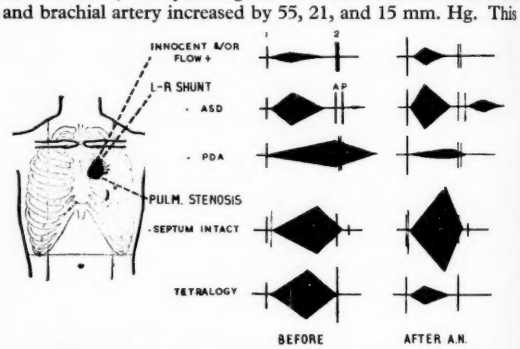

Fig. 8—The effect of amyl nitrite on pulmonary systolic murmurs of various causes.

was mainly due to the drop in arterial pressure, since the left ventricular pressure rose by only 15 mm. Hg in the first and third cases and fell by 17 mm. Hg in the second. The intensification of the murmur was slight in all cases. It would appear that the overdistended failing ventricle is unable to increase its systolic pressure in response to increased venous return. Amyl nitrite is best avoided in advanced cases of valve stenosis. In a patient with severe pulmonary stenosis prone to frequent anginal attacks, amyl nitrite provoked severe angina, presumably from overloading of the right ventricle. Even trinitrin sublingually aggravated the pain.

The effect of amyl nitrite appeared to be much less pronounced when there was pre-existing vasodilatation. This was most noticeable in 2 studies done during catheterisation under general anæsthesia. Despite the large dose of amyl nitrite given, very little effect occurred, presumably because of maximal systemic vasodilatation already present. When the vapour was given in the unanæsthetised state the usual response was elicited.

Discussion

The effect of amyl nitrite in mitral incompetence (Kahler 1932) and on innocent murmurs (Friedlander and Brown 1935, Mannheimer 1955, Paulin and Mannheimer 1957) has already been described, while its value in differentiating aortic stenotic from mitral incompetent murmurs was shown by Barlow and Shillingford (1958).

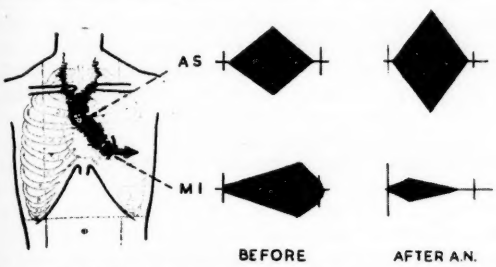

Fig. 9—The differentiation of aortic stenosis from mitral incompetence.
Amyl nitrite intensifies the aortic ejection murmur and shortens and softens mitral regurgitant murmur.

We have found amyl nitrite to be a valuable aid in the diagnosis of systolic murmurs in a number of situations.

Loud Parasternal Systolic Murmurs

Aortic and subaortic stenosis usually present little difficulty in diagnosis since their site, conduction, and in particular their character with mid-systolic crescendo and cessation well before the aortic sound, are sufficiently distinctive (fig. 9). The murmurs of pulmonary stenosis and small ventricular septal defects, however, may closely simulate each other, since pulmonary stenotic murmurs frequently extend into and beyond the aortic second sound and have a late crescendo, and thus resemble the pansystolic murmur of ventricular septal defect, which also may have a late crescendo and spill over the aortic sound (figs. 1 and 5). The site of maximal intensity of these murmurs often overlaps. Furthermore, in infundibular stenosis the murmur may be loudest lower down and then may be readily confused with ventricular septal defect. Pulmonary stenosis will be favoured if wide splitting of the second sound and a pulmonary ejection sound is heard. These signs are not always dependable, however, since wide splitting may occur in ventricular septal defect (personal observations), and a pulmonary ejection sound is usually absent in infundibular stenosis (Vogelpoel and Schrire 1959). Right ventricular hypertrophy on the E.C.G. will favour pulmonary stenosis but is often absent in milder cases.

When the auscultatory, electrocardiographic, and radiological features are equivocal the distinction between pulmonary or infundibular stenosis and ventricular septal defect may be impossible. This situation is all too frequent in infants and young children where auscultation and E.C.G. assessment of right ventricular hypertrophy is often much more difficult than in adults. Nevertheless, the diagnosis is readily made by the change in intensity of the murmur after amyl nitrite.

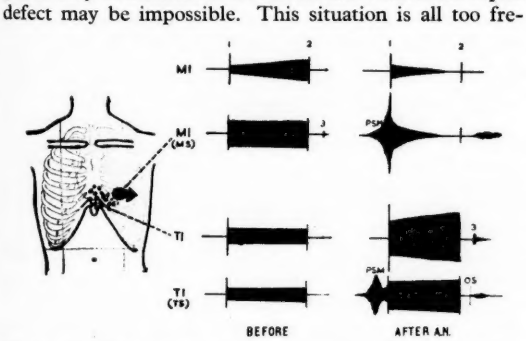

Fig. 10—The differentiation of mitral incompetence from tricuspid incompetence.
The mitral regurgitant murmur shortens and softens after amyl nitrite, while the tricuspid regurgitant murmur increases and may lengthen. The increased forward flow in both ventricles may elicit pathological murmurs, suggesting organic mitral or tricuspid valve disease.

The marked and prolonged intensification of the pulmonary or infundibular stenotic murmur at once excludes ventricular septal defect, where the murmur softens and shortens during and for some 20 seconds after the inhalation (figs. 1, 5, and 6). In acyanotic cases of Fallot's tetralogy the murmur also softens, but transient cyanosis often develops—thereby excluding simple ventricular septal defect. In large ventricular septal defects with large left-to-right shunts the systolic murmur often fails to soften, but such cases are readily recognised by associated signs. When mild stenosis is combined with small ventricular septal defect the diagnosis can be most difficult. This combination should be suspected when amyl nitrite induces equivocal changes—such as initial moderate softening, followed after 30 seconds by moderate intensification of the murmur.

Pulmonary or Infundibular Stenosis

In cyanotic cases of pulmonary or infundibular stenosis, the integrity of the ventricular septum is rarely in doubt. Thus severe stenosis with intact septum will have a very prolonged murmur, usually extending well beyond the aortic second sound, and very wide splitting, while in the tetralogy the murmur is much shorter, ending before or at the loud aortic second sound and splitting will be absent (Vogelpoel and Schrire 1955, 1958). In fact the severer the case the easier the diagnosis by auscultation alone. In mild or acyanotic tetralogy, however, the loud systolic murmur extends into and is loud at the aortic second sound, and there is frequently wide splitting because of an audible soft pulmonary second sound (Vogelpoel and Schrire 1955, 1958). Thus auscultatory and P.C.G. features may be indistinguishable from moderately severe pulmonary or infundibular stenosis with intact ventricular septum (fig. 7). The clinical, E.C.G., radiological, and catheter findings may also be identical. But this important diagnosis is easily settled by auscultation after amyl-nitrite inhalation, since the murmur gets much louder when the septum is intact and much softer and shorter in the tetralogy.

Cause of Pulmonary Systolic Murmurs

Pulmonary ejection murmurs due to increased flow without stenosis may be loud (fig. 8), especially in cases of atrial septal defect, but they usually end before the aortic component of the second sound, and should not be confused with the more prolonged murmurs of severe pulmonary stenosis. In mild pulmonary stenosis, however, the murmur may be indistinguishable from atrial septal defect and both conditions have wide splitting of the second sound, though the width varies normally with respiration in the former, and is "fixed" in the latter (Leatham and Gray 1956). A pulmonary ejection sound (Leatham and Vogelpoel 1954) is frequently present in mild pulmonary stenosis, but is rarely heard in atrial septal defect. Amyl nitrite intensifies the stenotic murmur much more than the flow murmur, but this is of little differential diagnostic value. A much more useful effect, however, is the marked increase of the mid-diastolic tricuspid flow murmur in atrial septal defect, bringing it out at times when even a deep inspiration fails to elicit it. The transient increase or emergence of this murmur therefore strongly favours atrial septal defect (or anomalous pulmonary venous drainage) as the cause of the pulmonary systolic murmur.

In patent ductus arteriosus with left-to-right shunt, but with high pulmonary vascular resistance (usual in infants), only a long systolic murmur may be heard in the pulmonary area. In such cases the diastolic component of the continuous murmur is absent or very short, because there is little or no pressure gradient between aorta and pulmonary artery during diastole; yet during systole an adequate pressure gradient persists, accounting for the long systolic murmur. Amyl nitrite proved most helpful in recognising such a case, since, unlike pulmonary ejection murmurs, the regurgitant ductus murmur diminished and shortened with the drop in systemic pressure (fig. 2). There is very little need for amyl nitrite when the typical Gibson murmur is present, but the marked reduction in intensity of both systolic and diastolic components of this continuous murmur may be useful in distinguishing it from other continuous murmurs. The continuous murmur of pulmonary arteriovenous aneurysm or fistula may simulate a patent ductus if cyanosis is missed and the murmur happens to be in the pulmonary area; it should, however, become louder after amyl nitrite, when the increased venous return and cardiac output increase the volume and speed of pulmonary blood-flow. The continuous murmur of a venous hum should seldom cause difficulty, but at times it may be mistaken for a patent ductus or a systemic arteriovenous fistula. Amyl nitrite greatly intensifies the venous hum but diminishes the murmurs of both the ductus and systemic arteriovenous fistula.

Other Systolic Murmurs

The use of amyl nitrite in differentiating aortic stenosis from mitral incompetence has been described by Barlow and Shillingford (1958). While the aortic ejection murmur is usually easily distinguished from the mitral regurgitant one, even when the aortic murmur is loud at the mitral area, there are times when distinction is difficult. Thus, if in mitral incompetence the aortic sound is buried in the murmur and a loud third sound is mistaken for it, the murmur may resemble an ejection murmur. Conversely, the aortic second sound may be so soft in aortic stenosis that only a systolic murmur is audible at the apex. The conducted aortic murmur may then be mistaken for a mitral regurgitant murmur on the grounds of a pansystolic murmur burying the aortic component. Amyl nitrite will differentiate the two murmurs, since the mitral murmur becomes shorter and softer, and the aortic murmur louder after inhalation (fig. 9). The test may fail when left ventricular failure is present and may be difficult to evaluate if there is atrial fibrillation. In combined aortic stenosis and mitral regurgitation the effect of amyl nitrite is to soften and shorten the mitral regurgitant murmur in the first 20 seconds, and to increase the ejection murmur after 30 seconds (Barlow and Shillingford 1958). But tight aortic stenosis may prevent the drop in left ventricular systolic pressure required to soften and shorten the murmur of associated mitral incompetence. In fact, it is likely that the left ventricular pressure will rise and then greatly increase regurgitant mitral flow and murmur and thus produce misleading effects.

In differentiating mitral incompetence from tricuspid incompetence there is seldom any difficulty, especially if the tricuspid murmur is strikingly augmented and lengthened by deep inspiration. Nevertheless, occasionally a case of tight mitral stenosis is rejected for valvotomy when a widely conducted tricuspid systolic murmur is mistaken for a marked mitral incompetence. In such situations amyl nitrite may aid diagnosis. The case with dominant mitral incompetence will develop a shorter and softer systolic murmur soon after amyl nitrite, whereas in tricuspid incompetence the murmur fails to soften and usually becomes louder (figs. 3, 4, and 7).

In cases with mitral systolic murmurs the decision whether the murmur is innocent or associated with valve disease is usually dependent on the presence of diastolic murmurs. Frequently all that is heard or shown on the P.C.G. is a loud third sound and a doubtful mid-diastolic murmur. After amyl nitrite, although regurgitant back flow diminishes with resultant softening of the murmur, forward flow is so accelerated that mid-diastolic and presystolic murmurs may emerge in striking fashion and this has been useful in deciding that the murmur is organic (figs. 3 and 10).

Similarly in tricuspid incompetence due to organic tricuspid valve disease amyl nitrite may elicit a striking tricuspid mid-diastolic and presystolic murmur, and even a tricuspid opening snap, all of which may be absent or doubtfully present on deep inspiration (figs. 4 and 10).

Is a Systolic Murmur Innocent or Not?

If a systolic murmur is loud, grade 3 or more (Freeman and Levine 1933), it is usually pathological; if it is softer it is often innocent provided there are no other abnormal signs.

There are at least three types of innocent systolic murmurs. A common variety is due to exaggeration of normal ejection vibrations.

They are always soft, of short duration, usually separated from the first sound by a short interval, reaching a crescendo before midsystole and ending well before the second sound, often slightly musical in quality, and usually loudest just internal to the mitral area. They are most frequent in childhood and may ultimately disappear. That they are ejection murmurs was shown by the increase in intensity following amyl nitrite in all 10 of our cases studied, confirming the observation of Paulin and Mannheimer (1957).

Differentiation from minimal aortic or sub-aortic stenosis can be most difficult, and amyl nitrite will not help. They may also resemble the short early systolic murmur heard in small defects in the muscular ventricular septum (Leatham 1958).

The short duration of the murmur in these cases has been attributed to closure of the defect when the ventricle is fully contracted. The true incidence of such defects may well be higher than realised since this type of case is seldom catheterised, and even if investigated the conventional techniques fail to detect a left-to-right shunt. Cineangiography with injection of contrast medium into the right ventricle under high pressure may demonstrate the defect (Jefferson 1959). Amyl nitrite should cause such murmurs to soften or even disappear and thus readily differentiate them from ejection murmurs. We have encountered 3 children with relatively short but loud parasternal systolic murmurs simulating an ejection murmur, but after amyl nitrite the murmur became much softer. We suspect that these patients have small muscular ventricular septal defects.

The innocent pulmonary systolic murmur is the second variety of innocent murmur. It is soft and short, best heard in the pulmonary area, and, though frequently heard in normal individuals, tends to be associated with hyperkinetic states (excitement, anæmia, thyrotoxicosis, pregnancy &c.). Paulin and Mannheimer (1957) attributed this murmur to turbulent flow through the infundibulum of the right ventricle. The innocent murmur is distinguished from the pulmonary systolic murmur of atrial septal defect by the absence of wide fixed splitting

of the second sound, and from pulmonary stenosis by its softness, lack of prolongation, and absence of wide splitting (fig. 8). Amyl nitrite causes a moderate increase in loudness during the phase of tachycardia and increased forward flow.

The third group of innocent systolic murmurs are the late systolic murmurs, usually loudest at the apex. They are not rare and frequently occur with a mid or late systolic click which may initiate the murmur. Since the click is considered to be pericardial in origin (Gallavardin 1913), the murmur might have a similar mechanism. The late systolic murmur needs to be differentiated from mild mitral regurgitation where the murmur is also maximal in late systole, and may even appear to be confined to late systole. However, it has been claimed that the P.C.G. will always demonstrate early systolic vibrations which will not be present in the innocent murmur (Leatham 1958). In 3 cases where a midsystolic click was associated with a late systolic murmur, amyl nitrite caused a temporary disappearance of the click, but the murmur increased in loudness and shifted its position to early systole during the first 30 seconds after inhalation. Whether this excludes mitral regurgitation must remain speculative, and the value of amyl nitrite requires further study in this type of murmur.

Summary

1. Inhaled amyl nitrite causes sudden vasodilatation resulting in a rapid fall in systemic blood-pressure, tachycardia, and increased cardiac output, followed by a greatly increased venous return to the right heart. The maximal hypotensive effect usually occurs at the end of a 30-seconds inhalation and persists 20–30 seconds after withdrawal of the ampoule; thereafter the pulse-rate and the blood-pressure gradually return to normal.

2. Left-sided regurgitant murmurs (mitral incompetence, ventricular septal defect, patent ductus arteriosus with a left-to-right shunt, and systemic arteriovenous fistula) became softer and shorter during and for some 20 seconds after the inhalation, the mechanism being dependent on the fall in systemic blood-pressure which reduced regurgitant flow.

3. Right-sided regurgitant murmurs (tricuspid incompetence) became louder and longer owing to the increased venous return to the right heart which increased regurgitant flow.

4. Left and right sided ejection murmurs, with the important exception of Fallot's tetralogy, increased in loudness because of increased forward flow. The intensification was greater and more sustained when the murmur was due to stenosis as opposed to increased flow without stenosis.

5. The chief value of the test was in the differential diagnosis of ventricular septal defect from pulmonary stenosis; pulmonary stenosis from mild or acyanotic Fallot's tetralogy; atypical patent ductus from other pulmonary systolic murmurs; aortic stenosis from mitral incompetence; and mitral incompetence from tricuspid incompetence, and in assessing whether a mitral or tricuspid systolic murmur was due to organic valve disease or not.

6. The test is simple and harmless and can be of great help in bedside diagnosis.

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PARKINSONISM DUE TO MIDBRAIN COMPRESSION

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THE current view of the pathology of parkinsonism is that degeneration of neurones is confined largely to the substantia nigra (Greenfield and Bosanquet 1953), although in the past the globus pallidus was thought to be affected also (Hunt 1917, Keschner and Sloane 1931, Neustaedter and Liber 1937, Davison 1942). In most cases the cause of the degeneration is unknown. In some it follows encephalitis lethargica, and it has been attributed occasionally to poisoning by carbon monoxide (Grinker 1926, Nielson 1943) or manganese (Canavan et al. 1934).

The association of parkinsonian manifestations with tumours of the brain has been mentioned rarely.

Bailey (1948) stated that parkinsonian tremor is rarely seen with brain tumours, and is of doubtful localising value. He cited a case in which parkinsonian masking and rigidity were associated with attacks of headache and vomiting; pneumoencephalography showed evidence of a midbrain tumour, but there is no mention that this was confirmed at operation or necropsy.

Mr. J. M. Small has previously allowed me to report a case in which parkinsonism appeared to be related to a cerebral meningioma (Oliver 1953). A man, aged 60, had been aware of a hard swelling in the right frontoparietal region for 6 months, during which time he had experienced giddiness on bending forward. For 2 months he had tended to fall to the right. He had a mask-like face; a left upper-neurone facial paresis; tremor of the mouth and limbs, with "pill-rolling" movements of the thumbs; cogwheel rigidity of the arms and lead-pipe rigidity of the legs; and left hemiparesis with a positive Babinski reflex. A large meningioma, embedded in the right frontoparietal cortex, was removed. After operation the hemiparesis recovered and the parkinsonian signs disappeared almost entirely. A year and 9 months later there had been no further change.

In my experience, parkinsonism is not uncommonly associated with intracranial space-occupying lesions,

although the physical signs are usually overshadowed. The three examples which follow suggest strongly that midbrain compression may often be the explanation.

Case-reports

Case 1.—A man, aged 51, was admitted to hospital on Jan. 9, 1956. 7 months previously he had had a jacksonian fit involving the right hand and lasting about 5 minutes. Afterwards, the hand was weak and clumsy for about 4 weeks. 6 weeks before admission he again became aware of weakness of the right hand, and for 3 weeks he had been dragging the right foot. 2 days previously he had an attack in which there was involuntary closure of the right hand (with a sensation like an electric shock in the hand) and elevation of the right arm; there was increased weakness of the hand after the attack.

The following abnormal physical signs were elicited: left conduction deafness; paresis of the right arm; absence of abdominal reflexes; paresis of the right leg; and increase of all tendon jerks with a positive Babinski response on the right.

Investigations.—Radiographs of the skull showed very pronounced vascular markings in both frontal regions, but they were wider and more numerous on the right. The calcified pineal gland was slightly displaced to the right. Radiographs of the chest were normal. Left carotid angiography showed, in the lateral views, downward curving of the anterior cerebral artery in the posterior frontal region; in the capillary and venous phases a well-circumscribed tumour "blush" corresponded with the downward displacement of the anterior cerebral artery. Biopsy through a posterior frontal burr-hole, examined by the frozen-section technique (Dr. P. M. Peters), showed the tumour to be a meningioma.

At *operation* on Feb. 23 I elevated a left frontal flap and removed the meningioma completely.

Postoperative course.—The weakness of the right arm and leg gradually receded, and the patient's general condition was satisfactory until the 7th day (March 3) when the following were observed: clouding of consciousness; expressive dysphasia; early papilloedema (there was none before operation); severe bilateral deafness; continuous parkinsonian tremor and cogwheel rigidity of both arms; return of paresis of the right arm; a positive Hoffman's sign on the left; absent abdominal reflexes; lead-pipe rigidity of both legs; weakness of the right leg; and bilaterally positive Babinski responses. Midbrain compression due to postoperative œdema of the left cerebral hemisphere was diagnosed. The fluid intake was restricted, and magnesium-sulphate enemas were given 6-hourly for 48 hours.

Except for slight cogwheel rigidity of the right arm, slight paresis of the right hand, and a positive Babinski sign on the right, the abnormal physical signs (including the tremor) had disappeared when the patient was discharged from hospital on March 15. On April 5 he had completely recovered, and he has since remained well.

Case 2.—A man, aged 35, was admitted to hospital on May 16, 1957. For 5 weeks he had had severe frontal headache worse in the mornings. Moderate papilloedema and slight incoordination of the left arm were observed.

Investigations.—Radiographs of the skull and chest, and electroencephalography were normal. Ventriculography showed dilatation of the lateral and third ventricles, and displacement of the fourth ventricle to the right.

Operation (Mr. Kenneth Paine) was performed through a vertical midline incision, with the patient sitting up. Bone including the posterior rim of the foramen magnum, was removed over the cerebellar hemispheres. A small opening was made in the dura mater over the left cerebellar hemisphere, and a brain cannula was passed through. Resistance was encountered at a depth of about 2 cm.; beyond that a cavity was entered, and about 50 ml. of yellow fluid was withdrawn (protein content 3·3 g. per 100 ml.). After the consequent reduction in intracranial pressure, a cruciate incision was made in the dura mater over the left cerebellar hemisphere, and the cerebellum was incised until the tumour was encountered. A large part of the tumour was removed piecemeal, but attempts to remove the medial part caused respiratory arrest, and this had to be left behind. When hæmostasis had been achieved, the cavity was filled with saline, *the dura mater was closed with interrupted sutures*, and the muscle layers and skin were sutured. Histologically the tumour was a grade-1 glioma (astrocytoma).

Postoperative course.—The morning after operation (May 24) consciousness was completely restored. The patient was able to move all his limbs normally, and to feed himself without assistance; his speech was slightly slurred. Next afternoon he had a temperature of 102·6°F. On May 26 the temperature was kept down to 100° by cooling; the patient was confused, there was nystagmus on looking to the right and no conjugate movement of the eyes to the left. On May 31 he was drowsy; lumbar puncture revealed xanthrochromic fluid under a pressure of 500 mm. of water. On June 3 he had parkinsonian tremor and cogwheel rigidity of the arms, and severe lead-pipe rigidity of the legs. On June 7 the conscious level had deteriorated; there was neck-stiffness, the tremor and rigidity were more pronounced, and he was dysphagic. The plantar responses were normal, and remained so. Tapping the ventricles produced clear fluid under a pressure of 200 mm., without pleocytosis. Lumbar puncture revealed slightly yellow, clear fluid under a pressure of 140 mm., containing 26 white cells per c.mm. His conscious level improved considerably after the pressure in the ventricle had been reduced to 90 mm. and in the lumber theca to 70 mm. At this stage he coughed persistently, diffuse rales and rhonchi were present, and appropriate antibiotics were given. From June 10 to 14 the intracranial pressure was reduced daily by ventricular and lumbar puncture.

On June 15 the patient was more conscious and he could swallow. The tremor was less, but the parkinsonian rigidity was worse, although muscular power was normal. On June 23 consciousness was completely regained, but the rigidity was so severe that flexion contractures were beginning in the right leg; muscular power was still normal. By July 22 contractures were beginning in the left leg.

At this stage the patient was transferred to the orthopædic department, where much work was done to prevent permanent contractures. By Oct. 29 he could walk with the help of tripod sticks; the parkinsonian tremor and rigidity were less severe. Improvement continued, and he returned to work as a council clerk on March 1, 1958.

When examined on April 6, 1959, his speech was monotonous; skilled movements, including writing, were slow; and there was slight incoordination of the left arm. Muscular power and tone were normal in all the limbs.

Case 3.—A man, aged 72, was admitted to hospital on Dec. 5, 1958. 5 weeks previously he had lost consciousness and collapsed in the street. He was soon able to walk to his doctor's surgery, accompanied by a friend. No abnormal physical signs were recorded and he was sent home to bed. He had frontal headache for a week and was kept in bed for 2 weeks. On Dec. 1 he again lost consciousness briefly, and fell to the floor. Next morning he had difficulty in speaking; the right arm was weak, and he could not see to the right.

On admission the abnormal physical signs were: confusion; nominal aphasia; right homonymous hemianopia; right upper-neurone facial paresis; flaccid paralysis of the right arm; absent abdominal reflexes; tremor at rest of the left arm and leg, with cogwheel rigidity of the left arm and lead-pipe rigidity of the left leg; a positive Babinski reflex on the right and an equivocal response on the left; and greatly increased tendon jerks on the left.

Ventriculography on Jan. 3, showed a large intracerebral frontoparietal tumour.

Biopsy (Mr. Bernard Fairburn) through a burr-hole revealed a grade-4 glioma (glioblastoma multiforme).

As the tumour was considered inoperable the patient was transferred back to the original hospital. He died on Feb. 13, 1959. In the left parieto-occipital region of the hardened brain was a glioblastoma. The globus pallidus was not obviously

invaded, but deep grooving of the uncus on both sides confirmed that the midbrain had been compressed.

Discussion

In case 1 œdema of the left cerebral hemisphere was diagnosed because of the onset, 7 days after operation, of drowsiness, motor dysphasia, papillœdema, and return of paresis of the right arm. Midbrain compression was indicated by the positive Hoffman and Babinski signs on the left (ipsilateral) side. The right-sided parkinsonian signs were associated therefore with œdema of the left cerebral hemisphere and the consequent midbrain compression, and they disappeared as the œdema subsided. (The severe bilateral deafness, probably due to compression of the medial geniculate bodies, also recovered.)

In the second case it is reasonable to conclude that cerebellar œdema developed 2 days after operation, and that compression of the brain-stem was rapid and severe because the dura mater had been sutured. The tremor and cogwheel and lead-pipe rigidity were probably caused by compression of the midbrain at the level of the tentorial opening, arising from upward herniation of an acutely swollen left cerebellar hemisphere. Compression of the midbrain by temporal-lobe herniation, as in cases 1 and 3, is well known (Kernohan and Woltman 1929), but compression by expanding lesions in the posterior fossa is less well known (Oliver and Gibbs 1952).

Case 3 had no parkinsonian tremor or rigidity either before the onset of symptoms due to the tumour or when the manifestations of the tumour were confined to the contralateral side. Ipsilateral tremor and rigidity developed when the level of consciousness declined, the ipsilateral tendon reflexes became brisker than those on the right, and the left plantar reflex became equivocal. One cannot argue that the tremor and rigidity were due to an effect on the globus pallidus, because they were ipsilateral.

Midbrain compression is the factor common to all three cases, and is the most likely explanation of the development of parkinsonian manifestations in association with some intracranial tumours. This would conform with current views on the site of the pathological process in both idiopathic and postencephalitic parkinsonism, and it is supported by the experimental work of Ward et al. (1948) who produced a parkinsonian tremor in monkeys by placing electrolytic lesions in the reticular formation of the midbrain. None of the patients had been given any drugs which could have caused parkinsonian phenomena.

Summary

Three examples of parkinsonian tremor and rigidity were associated with intracranial tumours.

These effects were probably brought about by compression of the midbrain—a view supported by the site of the pathological process in parkinsonism, and by the effects of lesions produced experimentally in the midbrain of monkeys.

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THE EFFECT OF DIURETICS ON PORTAL VENOUS PRESSURE

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THE interchange of fluid between the capillaries and the tissues depends upon the balance between hydrostatic and colloid osmotic forces. When this balance is disturbed in portal cirrhosis, by elevation of portal venous pressure and by reduction in plasma-albumin level, ascites develops. That this disturbance can in part be corrected by dietary sodium restriction and the use of diuretics has been known for many years.

Although the effectiveness of diuretics in controlling ascites formation is beyond doubt (Atkinson et al. 1954, Read et al. 1958), the mechanism by which they exert this action is uncertain, and the intervening steps through which increased renal loss of water and electrolytes is translated into loss of ascites is largely obscure. Diuretics might conceivably act by reducing plasma-volume, and thus lowering portal venous pressure, or by causing a temporary hæmoconcentration with a corresponding increase in plasma colloid osmotic pressure.

The object of this investigation was to decide whether diuretics influence portal venous pressure and plasma colloid osmotic pressure. Intrasplenic pressure has been used as a measure of portal venous pressure (Atkinson and Sherlock 1954), and estimation of serum-protein levels to detect changes in plasma colloid osmotic pressure.

Methods

Intrasplenic Pressure Technique

Intrasplenic pressure was measured by splenic puncture under local anæsthesia, using either the intercostal or subcostal route according to the size of the spleen. To minimise trauma to the spleen during respiration, pressures were recorded through a polyethylene tube introduced into the spleen by a method similar to that used for peripheral veins by Dotter and Smith (1958).

A piece of polyethylene tubing (1·1 mm. bore, 0·2 mm. wall thickness) was slipped over a lumbar puncture needle (1·0 mm. external diameter) and cut off to allow 1 cm. of tubing to project beyond the needle tip. The plastic tubing was then stretched tightly over the tip of the needle and cut off so that the needle tip projected about 3 mm. out of the tubing (fig. 1).

Fig. 1—Polyethylene tubing fitted over the outside of the needle before insertion into the spleen.

With the patient lying on his back, the needle with the polyethylene tubing fitted over it was inserted into the spleen. Correct positioning of the needle tip was indicated by blood dripping back when the stilette was removed from the needle. The needle was then withdrawn leaving the polyethylene tubing in the spleen. To avoid trauma to the spleen, the patient was asked to hold his breath until the needle had been withdrawn, after which he was allowed to breathe gently. Intrasplenic pressure was measured through the polyethylene tubing using a simple manometer filled with saline. If ascites was present, intra-abdominal hydrostatic pressure was measured after withdrawing the tubing from the spleen until its end lay in the peritoneal cavity. All pressures were related to a point 5 cm. below the level of the sternal angle.

TABLE I—EFFECTS OF DIURETIC THERAPY IN 10 PATIENTS WITH PORTAL CIRRHOSIS AND ASCITES

Case no.	Age (yr.)	Sex	Diagnosis	Drug and period of treatment (days)	Change in body-weight during treatment (kg.)	Serum				Ascitic fluid				Intra-splenic pressure (cm. H_2O)		Ascitic fluid pressure (cm. H_2O)	
						Albumin (g. per 100 ml.)		Globulin (g. per 100 ml.)		Albumin (g. per 100 ml.)		Globulin (g. per 100 ml.)					
						Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	49	F	Portal cirrhosis	Chlorothiazide 12	−7·3	3·2	3·2	2·9	3·4	1·0	1·2	0·7	0·9	37	19	13	7
2	45	F	„ „	„ 18	−6·4	2·7	2·8	3·2	3·4	0·5	0·8	0·3	0·3	32·5	22	10	
3	69	M	„ „	„ 24	−13·6	3·7	3·5	1·9	2·3	1·2		0·8		45	30	9	
4	75	F	„ „	„ 18	−10	2·5	2·7	2·5	2·1	0·55	0·4	0·8	0·6	37	17	10	5
5	45	F	Portal cirrhosis and ulcerative colitis	„ 15	−8·6	2·3	4·2	2·2	2·0					24	11		
6	45	F	Portal cirrhosis	„ 12	−0·9	3·0	3·2	3·7	3·5					53	41		
7	56	F	„ „	„ 12	+4·1	3·1	3·0	2·1	2·4	1·4	1·8	0·7	0·6	35	34	8	12
8	38	M	Portal cirrhosis	Mersalyl 14	+2·3	2·4	2·6	4·1	3·9	0·6	0·8	0·4	0·4	54	47	12	
			Ankylosing spondylitis Pulmonary tuberculosis	Chlorothiazide 17	+3·2	2·6	2·2	3·9	4·2					47	50		
9	52	F	Portal cirrhosis	Mersalyl 17	−6·4	3·5	3·9	2·1	2·3	1·7	1·5	1·8	1·4	50	33	8	5
10	50	M	„ „	„ 14	+6·4	2·7	2·5	3·9	3·6	0 3	0·5	0·5	0·6	52	42	12	15

Method of Investigation and Patients Studied

Ten patients with portal cirrhosis were investigated whilst undergoing treatment for ascites (see table I). Throughout the period of study the patients rested in bed, and were given a 22 mEq. sodium diet; daily weighing and measurement of fluid intake and urinary output were used to assess the response to treatment. In eight patients portal cirrhosis was uncomplicated, in one ulcerative colitis was also present and in one ankylosing spondylitis and pulmonary tuberculosis were additional features. After a control period of 5–10 days, intrasplenic pressure and ascitic fluid pressure were measured, and samples of blood and ascitic fluid were taken for albumin and globulin estimation. Treatment with diuretic was begun, and after 12–24 days these investigations were repeated. The diuretic used was chlorothiazide (2 g. daily) in seven patients and mersalyl by injection (2 ml. intramuscularly on alternate days) in two patients. The other patient received mersalyl for 14 days followed by chlorothiazide for 17 days.

Intrasplenic pressure was measured 5–12 days before and 2–4 days after paracentesis abdominis in three additional patients with portal cirrhosis and ascites while they were maintained on the low-sodium diet alone.

The effect of a single dose of 2 g. of chlorothiazide upon intrasplenic pressure was studied in eleven patients (table II) with portal hypertension. This was caused by portal cirrhosis alone in seven, by portal-vein thrombosis in three, and by hepatic venous occlusion (Budd-Chiari syndrome) in one. The only fluid allowed from 8 P.M. on the previous evening until the completion of the test at 5 P.M. was a single cup of tea with breakfast at 8 A.M. At 9 A.M. intrasplenic pressure was measured and 2 g. of chlorothiazide given by mouth in a single dose. 8 hours later intrasplenic pressure was measured again. The urinary output during the 8 hours after chlorothiazide was recorded. In two patients with ascites measurements of ascitic fluid pressure were made before and 8 hours after chlorothiazide.

Results

Clinical Observations

The clinical response to treatment (table I) was satisfactory in six patients, and in each diuresis occurred, ascites diminished, and body-weight fell. Ascites ceased to increase but did not diminish in one patient (case 6) during treatment, and the three remaining patients each continued to accumulate ascites despite treatment. During 11 periods of treatment in the ten patients, chlorothiazide was effective on 5 and ineffective on 3 occasions; mersalyl caused regression of ascites in one patient but failed in two others.

Serum Albumin and Globulin Levels

Little change in serum-protein levels was noted during the period of treatment in most patients. In several the serum-globulin rose slightly. Only case 5 showed a striking change in serum-albumin during treatment. In addition to portal cirrhosis and ascites this patient had ulcerative colitis, improvement in which probably accounted for the rise in serum-albumin from 2·3 to 4·2 g. per 100 ml. during treatment with chlorothiazide.

Ascitic Fluid Albumin and Globulin Levels

The total protein level before treatment exceeded 2·1 g. per 100 ml. in one patient only, and the ratio of albumin to globulin was often somewhat higher than in serum. In seven patients measurements were made before and after treatment with diuretics, and little alteration was noted.

As the protein levels of the serum and the ascitic fluid were virtually unaltered it seems reasonable to assume that the colloid osmotic gradient across the capillary walls was unaffected by treatment with diuretics.

Intrasplenic Pressure

Intrasplenic pressure fell during 10 of the 11 periods of treatment, reaching values within the normal range in 4. In general the patients with a satisfactory clinical response to treatment showed a greater reduction in intrasplenic pressure (fig. 2). This relationship held whether the patients were treated with chlorothiazide or with mersalyl. Some reduction of intrasplenic pressure was noted even in many patients who did respond clinically. In general, however, these patients had higher initial intrasplenic pressures, and, despite considerable reductions during

TABLE II—EFFECT OF A SINGLE DOSE OF CHLOROTHIAZIDE (2 G.) UPON INTRASPLENIC PRESSURE

Case no.	Age (yr.)	Sex	Diagnosis	Ascites	Intrasplenic pressure (cm. H_2O)		Urinary output (ml.) during 8 hours after chlorothiazide
					Before chlorothiazide	8 hours after chlorothiazide	
11	60	M	Portal cirrhosis	Present*	52	35	1230
12	51	M	„ „	Present†	40	36	360
3	70	M	„ „	Present	31	25	640
13	61	F	„ „	Absent	52	30	550
14	46	F	„ „	„	35	31	230
15	59	F	„ „	„	32	11	750
16	51	M	„ „	„	32	25	500
17	19	F	Portal cirrhosis with portal-vein thrombosis	„	39	14	920
18	26	M	Portal cirrhosis with portal-vein thrombosis	„	32	16	1120
19	61	M	Hepatic-vein obstruction	Present	31	28	880
20	55	F	Polycythæmia vera with portal-vein thrombosis	Absent	30	31	420

* Ascitic-fluid hydrostatic pressure: 10 cm. H_2O before chlorothiazide. 8 cm. H_2O 8 hours after chlorothiazide.

† Ascitic-fluid hydrostatic pressure: 6 cm. H_2O before chlorothiazide. 5 cm. H_2O 8 hours after chlorothiazide.

treatment, the final pressures were greater than those found in patients who improved clinically. Only in one patient (case 8) did intrasplenic pressure rise during treatment, and this coincided with rapid deterioration of his clinical condition.

The close relation between intrasplenic pressure and ascites formation was illustrated by case 1 (fig. 3).

During the period before treatment this patient accumulated ascites rapidly on a 22 mEq. sodium diet alone. Treatment

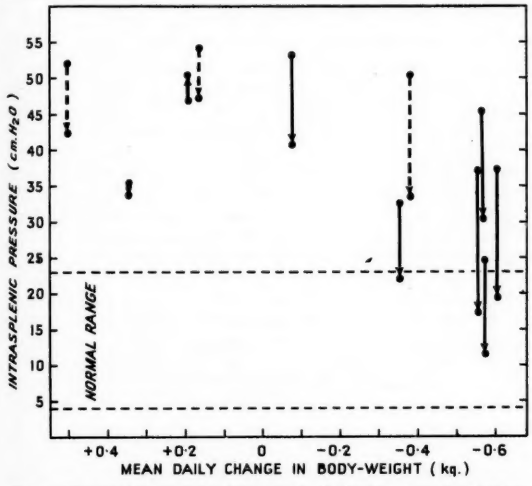

Fig. 2—Change in intrasplenic pressure during treatment of ascites with chlorothiazide (solid lines) or mersalyl (interrupted line), shown in relationship to the diuretic response, expressed as mean daily change of body-weight over the period of treatment.

The fall in intrasplenic pressure was most prominent in patients who responded best to treatment.

with chlorothiazide, supplemented by ammonium chloride, resulted in dramatic improvement with diuresis, loss of ascites, and a fall in body-weight. Intrasplenic pressure fell from 37 to 19 cm. H_2O. After discharge from hospital the patient stopped taking ammonium chloride on account of nausea and vomiting. The serum-chloride level fell, chlorothiazide ceased to be effective, and ascites rapidly reaccumulated. After readmission to hospital, it was found that the intrasplenic pressure had risen almost to its level before treatment and was 34 cm. H_2O.

Ascitic-fluid Hydrostatic Pressure

The possibility that the falls in intrasplenic pressure noted during diuretic therapy (table I) might be the effect of removal of ascitic fluid, with consequent reduction of intra-abdominal tension, was investigated by measuring ascitic-fluid hydrostatic pressure. Although no difficulty was encountered in making the initial measurements, after treatment the volume of ascitic fluid was often greatly diminished and its pressure frequently could not be measured with reliability. Nevertheless the readings which were obtained in cases 1 and 4 indicated that the reduction in intra-abdominal tension was very much less than that in intrasplenic pressure and in case 10, in whom ascites increased and ascitic fluid pressure rose, intrasplenic pressure nevertheless fell during treatment with mersalyl from 52 to 42 cm. H_2O. It therefore seemed most unlikely that the falls in intrasplenic pressure noted were the effect rather than the cause of the loss of ascites.

Intrasplenic Pressure Before and After Paracentesis

To determine to what extent intrasplenic pressure was related to intra-abdominal pressure, measurements were

TABLE III—EFFECT OF PARACENTESIS ABDOMINIS ON INTRASPLENIC PRESSURE

Case no.	Intrasplenic pressure (cm. H_2O)	
	Before paracentesis	After paracentesis
7	35	30
21	53	46
22	50	41

made before and after paracentesis abdominis in three patients (table III). In each instance abdominal distension was sufficient to cause discomfort. Drainage was continued until no more fluid could be obtained.

Some reduction in intrasplenic pressure was found in each of the three patients after paracentesis. This was small compared with that found in many patients treated with diuretics, despite the fact that the volume of fluid removed was generally greater after paracentesis. This indicates that reduction in intra-abdominal tension brought about by removal of ascitic fluid could only account for a fraction of the reduction in intrasplenic pressure caused by diuretics.

Effect of a Single Dose of Chlorothiazide on Intrasplenic Pressure

To determine the speed with which diuretics lower portal venous pressure, the effect of a single dose of 2 g. of chlorothiazide on intrasplenic pressure was studied (table II). 8 hours after giving the drug intrasplenic pressure had fallen by 16 cm. H_2O or more in five patients

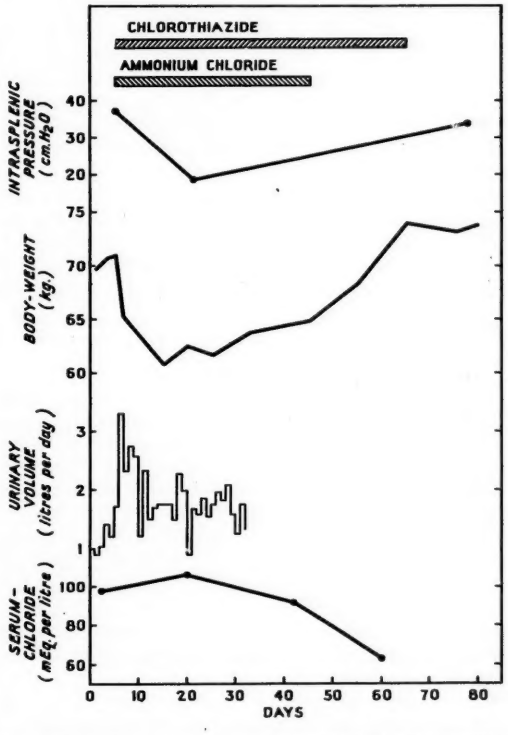

Fig. 3—Intrasplenic pressure shown in relationship to the regression of ascites during chlorothiazide therapy and its subsequent reaccumulation when the patient ceased to respond on account of chloride depletion.

Intrasplenic pressure fell to the normal range during the period in which the patient was responding to treatment but rose almost to its pre-treatment level as ascites reaccumulated (see text).

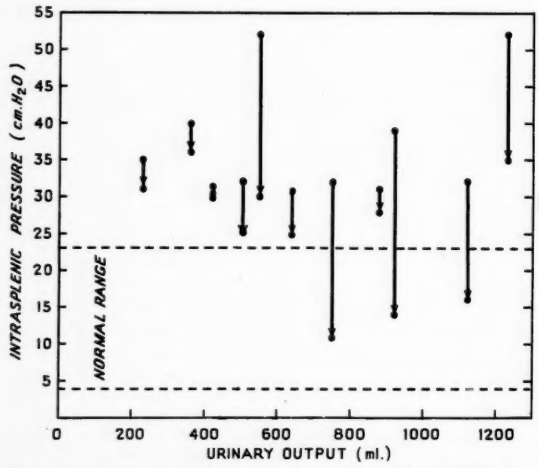

Fig. 4—Change in intrasplenic pressure over the 8 hours following a single dose of chlorothiazide (2 g.) shown in relationship to the diuretic response during this period.

The fall in intrasplenic pressure was greatest in patients showing the greatest diuretic response.

(including two with extrahepatic portal obstruction), and had reached the normal range in three of these. Intrasplenic pressure fell slightly in five of the six remaining patients, and in the sixth patient virtually no change in pressure occurred. Reduction of intrasplenic pressure following a single dose of chlorothiazide was seen both in patients with and in patients without ascites. In this small series of patients intrasplenic pressure fell more usually in those without ascites; four of seven patients without ascites showed a fall of 16 cm. H_2O or more in intrasplenic pressure compared with one of four patients with ascites.

In general the fall in intrasplenic pressure was related to the magnitude of the diuresis following chlorothiazide (fig. 4). When the urinary output did not exceed 500 ml. in the 8 hours following chlorothiazide, the intrasplenic pressure changed little, whereas five out of seven patients in whom the output exceeded 500 ml. showed a prominent fall in intrasplenic pressure.

Discussion

Except in one instance, the protein levels in the serum and ascitic fluid remained virtually unchanged, and it may be assumed that in these patients diuretics did not affect the colloid-osmotic gradient across the splanchnic capillary wall. Alteration of capillary permeability to protein has been suggested to contribute to the formation of ascites in portal cirrhosis. However, the total protein level in the ascitic fluid before treatment exceeded 2·1 g. per 100 ml. in only one patient. It therefore seems that capillary permeability was not abnormal. Certainly capillary permeability was unaltered during the period of treatment as the ascitic-fluid albumin and globulin levels showed little change.

The principal mechanism by which diuretics suppress the formation of ascites must therefore be by reduction of portal venous pressure, and probably their action is largely if not wholly explicable on this basis. That reduction in portal venous pressure is often effective in controlling ascites in portal cirrhosis has been demonstrated by the beneficial results of portocaval anastomosis in selected patients (Eisenmenger and Nickel 1956). In the present series the intrasplenic pressure following treatment appeared to be an important factor in determining the clinical response to treatment; when this had fallen to 33 cm. H_2O or less ascites regressed, whereas when intrasplenic pressure did not fall to this level ascites was not controlled. Intrasplenic pressure before treatment was in general higher in those patients who did not lose their ascites, and, although treatment with diuretics often did lower intrasplenic pressure, this reduction was apparently insufficient to prevent the formation of ascites.

The mechanism by which these drugs lower portal venous pressure is uncertain.

Chlorothiazide has been noted to lower arterial pressure (Wilkins 1957, Wilson and Freis 1958) and to increase the fall in blood-pressure caused by ganglion-blocking agents. This latter action is thought to be related to a diminution of plasma-volume following diuresis rather than any direct action of chlorothiazide on the blood-vessel wall (Dollery et al. 1959). Reduction in plasma-volume seems the probable mechanism whereby diuretics lower portal venous pressure, and, as such chemically dissimilar diuretics as chlorothiazide and mersalyl affect portal venous pressure, an action on the vessels themselves appears unlikely. Tapia et al. (1957) have demonstrated that chlorothiazide decreases plasma-volume and produces hæmoconcentration, both of which are enhanced by restriction of the dietary intake of sodium. The view that diuretics act in this way is supported by the observation that the fall in portal venous pressure after a single dose of chlorothiazide did show a rough correlation with the diuretic response. By a similar mechanism of decrease in plasma-volume, and consequent fall in portal venous pressure, restriction of the dietary intake of sodium may well reduce the rate of ascites formation.

Diuretics appear to offer a reliable and practicable means of controlling portal hypertension under clinical conditions. They are often effective within a few hours of administration, as was demonstrated by the reduction in intrasplenic pressure 8 hours after a dose of chlorothiazide. Diuretics often lower portal venous pressure in the absence of ascites, and in extrahepatic as well as intrahepatic portal obstruction. The variability of the reduction in portal venous pressure from patient to patient requires explanation and appears to depend chiefly upon variability of the diuretic response. This will be affected by hormonal mechanisms, particularly aldosterone which is excreted in increased amounts in portal cirrhosis with ascites and which antagonises the action of diuretics. A cause, more easily correctible, of failure to respond to these diuretics is a diminished plasma-chloride concentration, as was shown in case 1 (fig. 3). Nevertheless diuretics were effective in reducing portal venous pressure in most patients studied, and the magnitude of the reduction suggests that these agents may be of value in the management of portal hypertension presenting with bleeding from varices. Although the observations reported here were made over a short period, evidence is available that the reduction of plasma-volume and extracellular-fluid volume persists after many months' treatment with chlorothiazide (Wilson and Freis 1958), and probably the reduction of portal venous pressure would be equally persistent.

Summary

Using intrasplenic pressure as an index of portal venous pressure, measurements were made in ten patients with portal cirrhosis during treatment of ascites with chlorothiazide or mersalyl.

Intrasplenic pressure fell during treatment in every patient except one, and in four it reached normal levels.

The clinical response to treatment was related to the level of intrasplenic pressure after treatment and in each of the six patients in whom ascites was controlled the pressure fell to 33 cm. H_2O or less, whereas all the patients in whom ascites was not lost showed greater pressures than this after treatment.

Thus probably the principal mechanism by which diuretics relieve ascites is by reduction of portal venous pressure.

Measurements after a single dose of chlorothiazide showed that the fall in intrasplenic pressure occurred within 8 hours and was related to the diuretic response.

I wish to thank Mr. F. J. N. Powell, M.SC., A.R.I.C., for the plasma-protein estimations, and Dr. S. E. Cornford and Dr. J. L. Horner for assistance with the intrasplenic pressure measurements. I am indebted to Prof. R. E. Tunbridge, Prof. S. J. Hartfall, to Dr. A. Leese, Dr. R. N. Tattersall, Dr. D. Taverner, Dr. J. R. H. Towers, and Dr. G. Watkinson for kindly allowing me to study patients under their care.

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Addendum

Chlorothiazide has since been given to three patients with bleeding from œsophageal varices. In two, each of whom had had intermittent bleeding for 3 days, this ceased within 6 hours of starting the drug, which neither had received previously. In each, intrasplenic pressure fell to within normal limits in 8 hours after the commencement of treatment. The third patient had been taking chlorothiazide for the previous year because of ascites. Bleeding continued for 4 days despite continued administration of the drug, and intrasplenic pressure remained high (36 cm. H_2O).

SPORADIC GOITROUS CRETINISM

DEHALOGENASE DEFICIENCY IN THE THYROID GLAND OF A GOITROUS CRETIN AND IN HETEROZYGOUS CARRIERS

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DURING 1953 and 1954 we reported the results of radioactive-iodine (^{131}I) studies in non-endemic goitrous cretins. 8 of our patients were members of a family-group of itinerant tinkers. Our studies showed that the hypothyroid state in these cretins had developed despite an enlarged thyroid gland which was able and eager to trap iodide, to link it to protein, and to release it freely into the circulation. We suggested that a hormone precursor was being released; and that—since it was not metabolised usefully—it was excreted in the urine.

The sources of protein bound radioactivity in the serum of these patients were not then chemically identified, though we tentatively suggested that they might include an iodotyosine (McGirr and Hutchison 1953, Hutchison and McGirr 1954). In 1955 Stanbury and his colleagues in Leiden (Stanbury et al. 1955) demonstrated the presence of monoiodotyrosine (M.I.T.) and diiodotyrosine (D.I.T.) in the serum of a goitrous cretin. Later they showed that slices of thyroid tissue from such a case failed to deiodinate D.I.T. labelled with ^{131}I (Querido et al. 1956). They also showed that when labelled D.I.T. was given intravenously to 3 goitrous cretins over 60% was excreted unchanged in the urine (Stanbury et al. 1956). They concluded that the thyroid glands of their patients were unable to conserve the iodotyrosine because of a deficiency of the enzyme dehalogenase.

In 1956 we showed in 2 further cretins of our family-group the presence of M.I.T. and D.I.T. in the urine, and in 1 we found in the blood iodotyrosine as well as some thyroxine. We thought that this abnormal loss of iodotyrosines into the blood and urine was another effect of dehalogenase deficiency (McGirr et al. 1956); but we could not prove this, since the only patient in whom thyroidectomy was indicated refused operation.

Genetic studies showed that the presumed enzyme deficiency in our family-group was dependent on a single autosomal gene. The deficiency was recessive and produced frank clinical and biochemical abnormalities only in homozygotes (Hutchison and McGirr 1956). The parents of our patients and other presumed heterozygous carriers of the gene within the family-group all appeared normal. On the other hand, Stanbury et al. (1956) found that a goitrous cretin with the same defect had several euthyroid relatives with mild goitres, and that these presumed heterozygotes were less able than normal people to deiodinate the iodotyrosines.

Present Investigations

Our present studies round off the inquiry into our tinker family-group. First we investigated in more detail a cretin originally studied in 1951 (McGirr and Hutchison 1953, case 2). Second, we studied with radioactive M.I.T. 4 goitrous cretins, comprising 2 other members of the main tinker family-group and 2 other tinker siblings outside this family-group.

Chromatographic Investigation of Goitrous Cretin

This patient was first seen by us in 1951 when she was aged 11 years; treatment was started with dry thyroid (McGirr and Hutchison 1953). Though the thyroid was taken irregularly, in 1955 her bone age was normal and mentally she had much improved. She still had a large asymmetrical goitre. In the summer of 1958 she was seen by Mr. J. H. C. Philips, surgeon to Kettering General Hospital, Northampton, because her goitre had enlarged; and it was decided that thyroidectomy was justified. Mr. Philips kindly enabled us to study the iodine compounds in the thyroid gland, serum, and urine after an oral dose of 1 millicurie of ^{131}I given forty-eight hours before the operation. We were also able to study dehalogenase activity in the thyroid gland immediately after its removal.

Serum.—Blood samples were withdrawn three hours and forty-eight hours after the dose of ^{131}I. At forty-eight hours 89·0% of the total labelled serum-iodine was protein-bound, and 85·9% could be extracted by four washes of butanol at pH 2. Only 57·0% was thyroxine-like. Ascending chromatograms of butanol-extracts of serum, acidified to pH 2, were run in butanol acetic-acid solvent. After drying and staining of markers the chromatograms were scanned for radioactivity. In the three-hour chromatogram iodide and M.I.T. were clearly present, and there were traces of D.I.T. and thyroxine (fig. 1). The chromatogram of the forty-eight-hour serum was technically poor; such radioactivity as was recorded came from the D.I.T. and thyroxine zones, but these zones were not well separated.

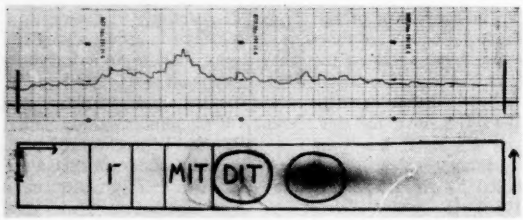

Fig. 1—Scan for radioactivity of ascending chromatogram of butanol extract of serum withdrawn three hours after oral ^{131}I (butanol acetic-acid solvent).

Urine.—Chromatograms of butanol extracts of urine passed during the periods 0–6 hours, 6–24 hours, and 24–48 hours were similarly prepared. They were run in butanol acetic-acid, butanol-ammonia, and collidine-ammonia solvents. In all chromatograms iodide, M.I.T., and D.I.T. were identified: other zones of radioactivity were due to several unidentified conjugates of the iodotyrosines. In the butanol acetic-acid chromatograms the amount of iodide was greatest in the first period; whereas the amount of conjugates towards the end of the strip, overlying the thyroxine-triiodothyronine zone, was greatest in the final period. Indeed, these conjugates came to contain more radioactivity than any of the other zones (fig. 2). The collidine-ammonia chromatogram showed many peaks of radioactivity some of which were no doubt due to acetic-acid, lactic-acid, and pyruvic-acid derivatives of the iodo-

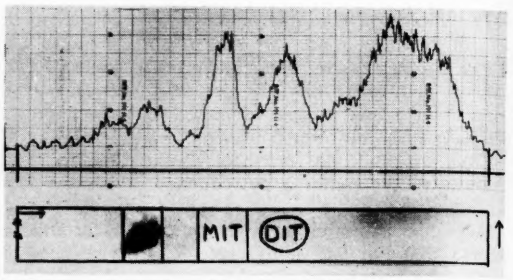

Fig. 2—Scan for radioactivity of ascending chromatogram of butanol extract of urine passed between twenty-four and forty-eight hours after oral ^{131}I (butanol acetic-acid solvent).

beyond the 3-5-diiodothyronine zone of the amyl-alcohol solvent (fig. 5). Elution of chromatograms prepared from the thyroid gland of a previous case of familial goitre, in which similar zones of radioactivity had been found, had established their common identity (unpublished observations).

Two slices of thyroid tissue, approximately 1 mm. thick, were incubated for eighteen hours at 37°C in Krebs-Ringer phosphate buffer (pH 7·4) which contained a trace of nicotinamide, and radioactive M.I.T. The experiment was performed in triplicate, with thyroid tissue from each lobe and from the isthmus. Chromatography of a butanol extract of the buffer fluid showed that virtually all the radioactivity persisted in the

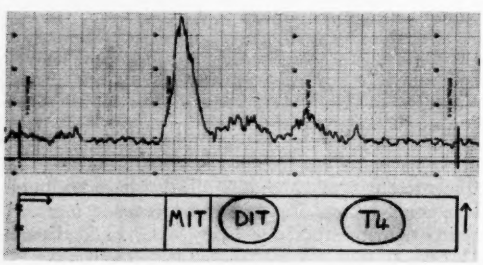

Fig. 3—Scan for radioactivity of ascending chromatogram of trypsin digest of thyroid tissue removed forty-eight hours after oral ^{131}I (butanol acetic-acid solvent).

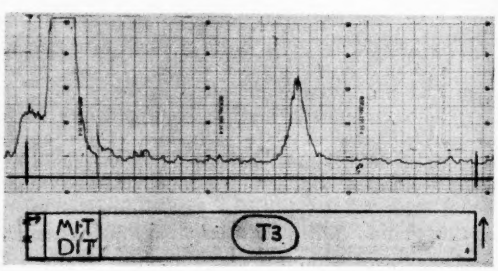

Fig. 4—Scan for radioactivity of ascending chromatogram of trypsin digest of thyroid tissue removed forty-eight hours after oral ^{131}I (butanol-ammonia solvent).

tyrosines. Without the appropriate markers their identity remains uncertain.

Thyroid.—Portions of the thyroid gland were homogenised and digested by trypsin in a barbitone buffer at pH 8·6. Ascending chromatograms of the digest were run in butanol acetic-acid, butanol-ammonia, and amyl-alcohol solvents. When the chromatograms were scanned for radioactivity M.I.T. and D.I.T. were identified but no thyroxine was detected. A zone of radioactivity, the chemical source of which is not known, was present in chromatograms run in each of the three solvents. This zone was located between D.I.T. and thyroxine in the butanol acetic-acid solvent (fig. 3), beyond the triiodothyronine zone of the butanol-ammonia solvent (fig. 4), and

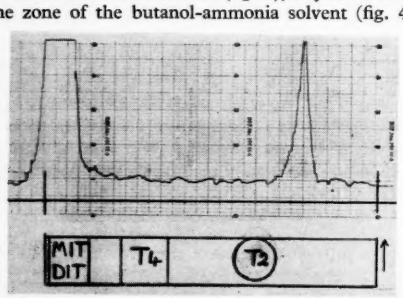

Fig. 5—Scan for radioactivity of ascending chromatogram of trypsin digest of thyroid tissue removed forty-eight hours after oral ^{131}I (amyl-alcohol/2*N* NH_4OH solvent).

M.I.T. zone, and no radioactivity appeared in the iodide zone (fig. 6). The dehalogenase activity of the thyroid gland was negligible or absent.

Radioactive M.I.T. Studies of Dehalogenase Activity

We obtained the cooperation of 4 goitrous cretins or their guardians and were able to examine their dehalogenase activity by a modification of the technique described by Stanbury et al. (1956). 2 of these patients (cases 1 and 2) were members of the main tinker family-group. 2 (cases 3 and 4), who were also

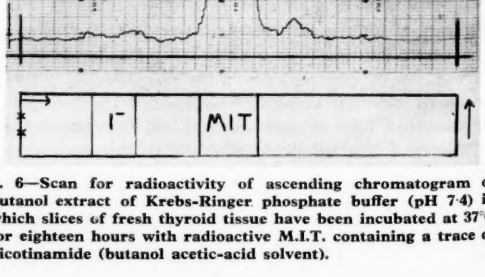

Fig. 6—Scan for radioactivity of ascending chromatogram of butanol extract of Krebs-Ringer phosphate buffer (pH 7·4) in which slices of fresh thyroid tissue have been incubated at 37°C for eighteen hours with radioactive M.I.T. containing a trace of nicotinamide (butanol acetic-acid solvent).

URINARY EXCRETION OF RADIOACTIVE MONOIODOTYROSINE AFTER AN ORAL DOSE OF LABELLED L-MONOIODOTYROSINE

	Diagnosis	No. of cases	M.I.T. + M.I.T.-conjugate as % of ^{131}I in urine		M.I.T. + M.I.T.-conjugate as % of dose		
			0–2 hr.	2–6 hr.	0–2 hr.	2–6 hr.	0–6 hr.
Controls	Euthyroid ..	5	0–17·6	0–10·2	0–3·3	0–2·5	0–5·7
	Primary myxœdema	3	0–9·5	0–10·2	0–1·1	0–2·3	0–3·4
	Non-toxic goitre	5	0–14·1	0–7·7	0–1·1	0–2·2	0–3·3
	Range		0–17·6	0–10·2	0–3·3	0–2·5	0–5·7
	No.	Sex	Age (yr.)				
Tinker cases	1	F	39 months		75·0	100·0	6·2	24·7	30·9
	2	F	26		100·0	98·2	19·6	22·0	41·6
	3	M	10		23·8	67·4	5·1	23·7	28·8
	4	F	9		100·0	64·6	14·4	21·9	36·3
	5	M	19		14·2	37·0	1·7	5·0	6·7
	6	M	28		13·9	34·8	1·0	8·7	9·7
	7	F	10 weeks		31·7	24·7	..	..	..
	8	F	17 weeks		42·8	13·3	..	..	..

of tinker origin, came from a home for deprived children (Hutchison and McGirr 1956); and so we were unable to link up their ancestry with the pedigree of the main group. We were also able to study 4 euthyroid members of the main tinker family-group. 2 of them (cases 5 and 6) were apparently healthy, and neither had a goitre. Case 6, who was the husband of case 2, was also her cousin. Case 5 was the nephew of cases 2 and 6. Case 7 was a 10-week-old female infant, the niece of the patient described in this paper. She had been admitted to hospital at seven weeks with pyloric stenosis and had made a good recovery. She was euthyroid and non-goitrous. Case 8 was a 17-week-old infant, the second child of a goitrous cretin (case III 23, Hutchison and McGirr 1956), who had married outside the tinker family-group. She had been admitted to hospital two weeks earlier with malnutrition. On examination she was euthyroid and non-goitrous.

The 13 control cases included 5 patients without thyroid disease, 3 with primary myxœdema, and 5 with non-toxic nodular goitre.

An oral dose of 5–25 microcuries *l*-monoiodotyrosine labelled with ^{131}I was administered to the patients, and their urine was collected during the next six hours in two periods (0–2 hours and 2–6 hours). The total excreted radioactivity was measured: and a sample from each period was examined by ascending chromatography in butanol acetic-acid solvent after acidification and butanol extraction. The strips were scanned for radioactivity and the proportion present as M.I.T. was then estimated by planimetry (see table).

In the controls less than 6% of the radioactive M.I.T. appeared in the urine as free or conjugated M.I.T. The most ^{131}I that was passed in either of the two periods as M.I.T. was 17·6%.

The findings in the 4 goitrous cretins were notably different. 28% or more of the M.I.T. appeared in the urine as free or conjugated M.I.T. The relative proportion of the ^{131}I excreted as M.I.T. was strikingly higher (see table).

The results in the 4 apparently normal tinkers fall between the two groups. In the 2 who were continent the amounts of M.I.T. excreted as free or conjugated M.I.T. were only slightly higher than in the controls group, but ^{131}I excreted as M.I.T. was at least 31·7% in one of the two periods for each of the 3 subjects.

Discussion

The ^{131}I tests performed in 1951 on the goitrous cretin here described showed great avidity for iodide in the thyroid: this is common to various types of goitrous cretins (Stanbury and McGirr 1957, Hutchison 1958). Failure to discharge ^{131}I from the gland by potassium thiocyanate established that the trapped ^{131}I was oxidised to iodine and incorporated in thyroglobulin in combination with tyrosine. The serum-^{131}I fractions were not studied in this patient in 1951. In 1958 89·0% of the serum-^{131}I was proteinbound; and, while 85·9% was butanol-extractable, only 57·0% was thyroxine-like. This, and the chromatographic finding of M.I.T. and D.I.T. in the serum and of the iodotyrosines and their conjugates in the urine, strongly suggest that the proteinbound ^{131}I includes something other than thyroxine. This view is in agreement with the results of earlier studies in 2 other related goitrous cretins (McGirr et al. 1956) and points to a dehalogenase deficiency.

In the present patient, for the first time in our series of investigations, we were able to examine the thyroid gland itself which had been removed at operation. The complete failure of this tissue, under standard conditions in vitro, to deiodinate M.I.T. labelled with ^{131}I suggests a lack of dehalogenase activity within the thyroid gland. By the same technique dehalogenase activity in thyroid tissue could be demonstrated in 2 adult patients with non-toxic nodular goitres and in 2 children with goitres due to other enzyme defects. The thyroid tissue from these patients deiodinated more than 90% of the radioactive M.I.T. Only on one other occasion in our experience —in a young goitrous girl in whose serum and urine iodotyrosines were also identified—have fresh thyroid slices failed to deiodinate M.I.T. (McGirr et al. 1959). These findings confirm that the fundamental biochemical defect in our patient and in the 12 other goitrous cretins whom we have now traced in her family-group is diminished or absent dehalogenase activity; and we believe that the goitre and hypothyroidism in these patients may have been caused by the consequent loss of the iodotyrosines and their iodine from the thyroid gland. Even considerable hyperplasia—presumably under the influence of thyrotropin secreted in response to inadequate production of thyroid hormone—has failed to maintain these patients in a state of euthyroidism. The abnormally high serum-thyrotropin in a goitrous cretin from the main tinker family-group has been confirmed by biological assay (unpublished data).

In the chromatograms prepared from the trypsin digests of the thyroid there are three findings of note. First, radioactivity in M.I.T. greatly exceeded radioactivity in D.I.T.: the M.I.T./D.I.T. ratio varied from 2·91 to 4·00 in different portions of the gland. These ratios differ from those found by Pitt-Rivers et al. (1957) in normal human thyroids (0·5–0·75), but they are similar to the ratios found by these workers in non-toxic nodular goitres and by ourselves in goitres from children with other enzyme defects. They contrast with the urinary chromatographic findings in the same patient where the amount of radioactivity in D.I.T. exceeded that in M.I.T. Secondly, no thyroxine was detected in the thyroid tissue. While this finding is consistent with difficulty in the oxidative coupling of two molecules of D.I.T. to form thyroxine, the proved absence of dehalogenase activity makes it more probable that the rapid excretion of such thyroxine as was synthesised prevented storage in the gland. Defective coupling of the iodotyrosine, moreover, would point to a deficiency of an oxidative enzyme, in addition to the absent dehalogenase; and that one gene should be responsible for two enzymes is contrary to modern genetic concepts. Finally, an unidentified zone of radioactivity was present in chromatograms run in each of the three solvents used. We are satisfied from elution experiments that the three zones represent the same substance: we have now found it in a goitrous cretin, in a euthyroid patient with familial goitre, in a patient with Hashimoto's disease, and in 5 patients with nodular goitre; but we do not know its chemical identity or its significance.

We have demonstrated in 2 other goitrous cretins of the patient's family-group, and in 2 goitrous and cretinous siblings who were also of tinker stock, impaired ability to deiodinate orally administered radioactive M.I.T. This impaired dehalogenase activity in the 2 pairs of tinker cretins supports our belief that they have a common ancestry (Hutchison and McGirr 1956). The results of the radioactive M.I.T. excretion tests also suggest an impaired ability to deiodinate M.I.T. in 4 apparently euthyroid relatives of the goitrous cretins of the main tinker family-group. The results of similar tests in another patient and in her mother, whose thyroids failed to deiodinate M.I.T., support this opinion (McGirr et al. 1959). In the first six hours after its administration 54·3% of the dose of M.I.T. appeared in the urine of this patient in free or conjugated form. M.I.T. or its conjugates accounted for 97·3% of the ^{131}I in the urine during the 0–2-hour period and for 96·1% during the 2–6-hour period. The mother, who was euthyroid and non-goitrous, excreted 14·3% of the dose as free or conjugated M.I.T. during the first six hours: M.I.T. or its conjugates accounted for 43·4% of the ^{131}I in the urine during the 0–2-hour period and for 1·0% during the 2–6-hour period.

It is reasonable to assume that—whereas patients with goitre and frank hypothyroidism are homozygous—their relatives, who show only minor biochemical abnormalities, are heterozygous carriers of the incompletely recessive gene. Our results with radioactive M.I.T. show that this technique allows the unmasking of heterozygous carriers as well as of frankly abnormal cases. The selfcontained existence of the tinker folk suggests that they would be a fertile group for genetic studies with a simple test such as we have employed. Unfortunately it has proved difficult so far to win sufficient cooperation in a city remote from their usual haunts. Perhaps a field-trial would prove more successful.

Summary

Absence of dehalogenase activity has now been directly demonstrated in the thyroid gland of a goitrous cretin. She is a member of a family-group in which goitrous cretinism is transmitted as a simple recessive characteristic.

Chromatographic analysis of thyroid tissue from this patient showed an abnormally high monoiodotyrosine/diiodotyrosine (M.I.T./D.I.T.) ratio, absence of thyroxine (probably due to rapid excretion and failure to store), and a chemically unidentified zone of radioactivity previously encountered in other forms of goitre. The significance of this zone is unknown.

Impaired ability to deiodinate radioactive M.I.T., which was found in 2 other goitrous cretins of the patient's family-group and in 2 goitrous cretins who were also tinkers, suggests a common ancestry. A similar but lesser defect in deiodinating M.I.T. was demonstrated in 4 apparently healthy members of the main family-group. It is suggested that these are heterozygous carriers of the incompletely recessive gene.

The ability to detect heterozygotes in a genetically determined disease may have practical application in genetic counselling.

This work has been supported by grants from the Scottish Hospital Endowments Research Trust and received financial assistance from the Rankin fund of the University of Glasgow. The serum-thyrotropin assay was carried out for us by Miss Judith R. Brown, B.SC., of the clinical endocrine research unit (Medical Research Council), University of Edinburgh.

References at foot of next column

SERUM-AMYLASE LEVELS DURING STEROID THERAPY

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STUDIES on rabbits have suggested that administration of cortisone may be followed by changes in the non-islet tissue of the pancreas. Stumpf et al. (1956) described acinar lesions and peripancreatic fat necrosis in many rabbits which had received large doses of cortisone, and this was confirmed by Bencosme and Lazarus (1956). Stumpf et al. also found a considerable rise in the blood-amylase levels in 34 of 36 cortisone-treated rabbits with these pancreatic lesions. Postmortem studies by Carone and Liebow (1957) on 54 patients treated with cortisone or related substances revealed similar histological findings in many. Neither Stumpf et al. nor Carone and Liebow noted any correlation between the incidence of such lesions and the amount or duration of therapy.

The mechanism has been postulated by Bencosme and Lazarus (1956) as obstruction to the pancreatic ducts due to the steroids inducing altered viscosity of the pancreatic secretion or proliferation of the duct epithelium. On the other hand, Stumpf et al. (1956) suggested that the hyperlipæmia produced by cortisone may cause the pancreatic changes.

The changes are similar to those observed in acute pancreatitis (*British Medical Journal* 1958), and this may offer some clue to the ætiology of this disease. But few cases of acute pancreatitis complicating steroid therapy have been described (Zion et al. 1955, Baar and Wolff 1957, Marczynska-Robowska 1957), though in these the diagnosis was confirmed at necropsy. Recently Bourne and Dawson (1958) reported a case from this hospital in which acute abdominal pain occurred in conjunction with an elevation of the serum-amylase several weeks after therapy with prednisolone was started for the nephrotic syndrome. If pancreatitis does complicate treatment with steroids it must seldom declare itself clinically, and in Carone and Liebow's (1957) series there was no definite evidence during life to suggest pancreatic disease.

The importance of changes in the serum-amylase level in patients under treatment with steroids has been emphasised (*Lancet* 1957), and I decided to investigate the problem.

Investigation

All patients treated with steroids had their serum-amylase estimated at least once. The drugs were mainly prednisolone, cortisone, or corticotrophin, but some patients had prednisone, triamcinolone, hydrocortisone, dexamethasone, or methylprednisolone; these were given orally or intramuscularly except in 1 case where rectal hydrocortisone supplemented oral therapy. Several patients had more than one drug. The usual doses were given except for 1 patient who had had 200–600 mg. of

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DR. MCGIRR AND OTHERS: REFERENCES

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cortisone per day for about six years. The duration of treatment before the serum-amylase estimations was from one to six years in 4 cases, from a month to one year in 10, and for several days to one month in the others. This series includes a case of Cushing's disease of about ten years' duration, and in 2 patients the drugs were used as replacement therapy. Cases were excluded from the series when a raised serum-amylase was found to be associated with urea retention, or when pancreatitis was suspected before therapy. In most cases the serum-amylase was estimated only once; in the others serial levels were determined.

Serum-amylase was estimated by the method of Street and Close (1956), using amylose as a substrate. The normal range is from 6 to 33 Street-Close (S.C.) units (Close and Street 1958). Rapid, simple, and reproducible, this method is not subject to the potential error of the Somogyi technique, which gives results that vary with the blood-sugar level (Street 1958).

Results

The serum-amylase levels of 38 patients (11 males, 27 females) on steroid therapy were compared with the figures of Street and Close (1956) derived from 101 hospital patients with no suspected pancreatic disease. When more than one estimation had been made a single result was chosen at random. A small but significant difference was observed between the mean values of the two groups.

"Steroid" group	22·79
Control group	18·88 ($p < 0·01$).

In 4 patients the serum-amylase was just outside the normal range; the highest of these results was 39 S.C. units, and this patient had a pretreatment level of 21 S.C. units.

In a 5th patient the serum-amylase levels ranged from 36 to 89 S.C. units.

This man, aged 83, with rheumatoid arthritis, had been treated with prednisolone 5 mg. daily for several months. The highest blood-urea level recorded was 47 mg. per 100 ml. He had experienced periodic abdominal pain of "ulcer" type for about ten years. A deformed duodenal cap, but no ulcer, had been demonstrated. It seemed unlikely, though not impossible, that pre-existing pancreatic disease would account for the considerable rise in serum-amylase, and steroid therapy may well have been responsible.

Discussion

These findings show that the frequency and extent of the rise of serum-amylase noted by Stumpf et al. (1956) in cortisone-treated rabbits is not equalled in man, at least with the usual doses of steroids. The rabbits received a daily dose of 3–8 mg. cortisone per kg. body-weight for twenty-one to eighty-one days, either continuously or intermittently, and in man equivalent doses are seldom prescribed. But the patients studied post mortem by Carone and Liebow (1957) had had the usual amount of steroids; these workers found the histological changes of acute pancreatitis or fat necrosis in about 30%, with other changes in over half. As almost all the cortisone-treated rabbits with pancreatic lesions had moderately or grossly elevated serum-amylase levels, it seemed reasonable to expect an appreciable rise in serum-amylase in many patients in this series. That the rise was very slight may be because only mild lesions were produced by the steroids; in only 3 of Carone and Liebow's 54 cases were they described as "severe".

The small though statistically significant rise is very difficult to interpret, and it would be hazardous to attribute it simply to the action of the steroids on the pancreas. Serum-amylase levels clinically acceptable as indicative of pancreatic disease were found in only 1 case.

Summary

The serum-amylase levels of 38 patients treated with steroids for various conditions were compared with those of a control group.

A statistically significant rise was found in the group having steroids; but it was so slight that there was doubt whether pancreatic lesions could be responsible.

In 1 case a grossly elevated serum-amylase level may have resulted from steroid therapy.

I wish to thank Dr. R. A. Robb of the Mathematics Department, Glasgow University, for the statistical analysis.

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Preliminary Communications

THE DETECTION OF PLACENTAL DEGENERATION DURING PREGNANCY

SERUM-ISOCITRIC-DEHYDROGENASE ACTIVITY

IT is generally accepted that pre-eclamptic toxæmia is often associated with a small infarcted placenta. Radio-active-tracer studies have shown considerable reduction in uteroplacental blood-flow in this condition,[1 2] and the high fœtal mortality is attributed to "placental insufficiency". Histological examination of such placentas discloses a marked acceleration of the degenerative changes which normally take place in the villi towards term, but no lesion characteristic of pre-eclamptic toxæmia.[3]

Leakage of various enzymes from autolysing cells has been widely used as an index of damage in necrosis of heart and liver. The placenta is a rich source of the soluble enzyme isocitric dehydrogenase. This enzyme is present in most tissues and is a component of the tri-carboxylic acid cycle. Sterkel et al.[4] studied the serum activity of this enzyme in various diseases and found great increases in viral hepatitis and moderate increases in chronic liver disease. It was not raised in a great variety of other conditions including myocardial infarction. They also recorded normal values in five normal pregnant women at term.[5]

Recent work in this laboratory has shown increases in serum-isocitric-dehydrogenase activity in a wide variety of toxic liver injuries in the rat.[6]

We have measured isocitric dehydrogenase (I.C.D.) activity in the serum in the latter half of pregnancy in

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SERUM-I.C.D. ACTIVITY IN NORMAL PREGNANCY AND PRE-ECLAMPTIC TOXÆMIA

Clinical data		Serum-I.C.D. activity (units)
12 normal pregnant women (24–40 weeks)		1·7±0·6
Pre-eclamptic toxæmia	Blood-pressure (mm. Hg)	
A	150/95	8·3
B	180/120	18·0
C	150/100	10·3
D	180/120	6·6
E	150/100	5·0
F	180/110	5·3
G	130/100	1·0
H	140/90	2·4

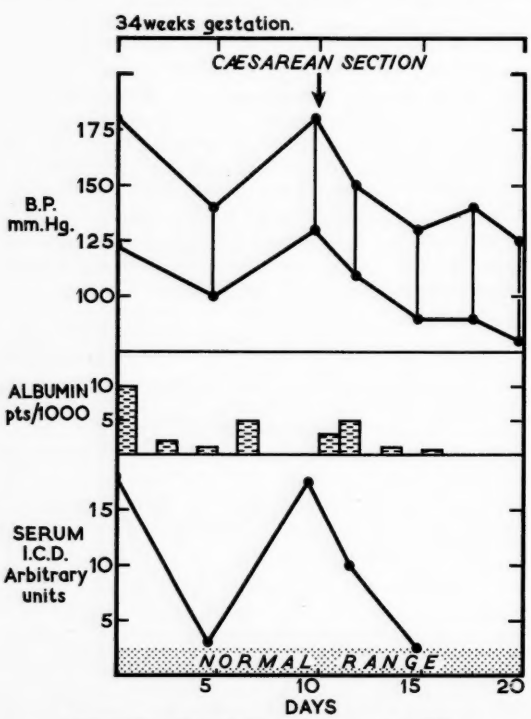
normal women and in women with pre-eclamptic toxæmia in an attempt to detect placental degeneration before delivery.

METHOD

Serum-I.C.D. activity was measured by a modification of the method of Wolfson and Williams-Ashman.[5] Serum obtained at routine venepuncture was used. Serum showing any hæmolysis was rejected.

Materials.—Triphosphopyridine nucleotide (T.P.N.) and sodium isocitrate were products of the Sigma Chemical Co., St. Louis, Missouri.

Assay system.—The components of the system were as follows: Tris buffer, pH 7·4, 0·033 *M*, T.P.N. 0·0001 *M*, sodium isocitrate 0·0017 *M*, sodium chloride 0·015 *M*, manganese sulphate 0·001 *M*, serum 0·5 ml. This was made up to a final volume of 3·0 ml. with water. The components, with the exception of T.P.N., were pre-incubated for at least 60 minutes at 20°C, because of transient initial changes in turbidity on dilution of the serum. The reaction was started by the addition of T.P.N. to one tube and read against a blank containing no substrate and no T.P.N. The increase in absorption at 340 mμ was followed in a Unicam SP500 spectrophotometer in silica cells with a 1 cm. light path at 20°C. Readings were made at frequent intervals for at least 30 minutes and the increases in absorption were linear with time. Results are expressed in arbitrary units, where 1 unit is the amount present in 1 ml. of serum causing an increase in absorption at 340 mμ of 0·001 per minute.



Severe pre-eclamptic toxæmia in a woman of 34.

RESULTS

The table shows that in some cases of pre-eclamptic toxæmia there is an increase in serum-I.C.D. activity. The criteria for a diagnosis of pre-eclamptic toxæmia were the development of a blood-pressure greater than 140 mm. systolic or 90 mm. diastolic, accompanied by albuminuria or œdema, in women with normal blood-pressures during the early months of pregnancy. These cases may include some patients with essential hypertension with superimposed pre-eclamptic toxæmia. It can also be seen that not all cases with a raised blood-pressure have increased serum-I.C.D. activity. An increase in serum-I.C.D. activity indicates only recent degeneration (probably within the past forty-eight hours).

The accompanying figure shows the changes in serum-I.C.D. activity in a case of severe pre-eclamptic toxæmia. The initial very high reading fell almost to normal after five days' treatment with hypotensive drugs and bed rest. The subsequent clinical deterioration with a rising blood-pressure was accompanied by a great increase in serum-I.C.D. activity. Cæsarean section was performed because of impending eclampsia. The placenta weighed only 290 g. and on histological examination showed extensive old and recent degenerative changes. The baby weighed 1700 g., and mother and child subsequently did well. Serum-I.C.D. activity and the blood-pressure returned rapidly to normal. It is clear from this case that even in severe pre-eclamptic toxæmia the serum-I.C.D. activity might be normal at any one moment, regardless of the blood-pressure readings.

CONCLUSIONS

In this small series the correlation between serum-I.C.D. activity and the height of the blood-pressure is not absolute. In addition, values above normal have been found in some cases of accidental hæmorrhage and in women with previous intrauterine death associated with pre-eclamptic toxæmia but normal blood-pressures during the present pregnancy. It is suggested that, in the absence of liver disease, an increase in serum-I.C.D. activity indicates the presence of active placental degeneration during pregnancy. Single elevated readings indicate only the presence of active placental degeneration without giving any indication of the residual functioning placenta. Serial elevated readings, however, may show progressive placental degeneration in pre-eclamptic toxæmia and possibly in postmaturity. These are situations in which the reserve of placental function is critical for fœtal survival. A rise in serum-I.C.D. activity is not an indication for interference, but in certain cases it may help the obstetrician to know that there is progressive placental degeneration. Further work is in progress to extend these observations and to evaluate their significance in relation to clinical findings, fœtal and placental weight, and the presence of degenerative changes in the placenta.

It is a great pleasure to acknowledge the advice and cooperation of Prof. W. C. W. Nixon and the staff of the Obstetric Hospital, University College Hospital. Our thanks are also due to Sir Roy Cameron, F.R.S., for his interest and encouragement. The expenses of the investigation were met from the Graham Research Fund of the University of London.

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URINARY PREGNANETRIOL THROUGHOUT THE MENSTRUAL CYCLE

OBSERVATIONS ON A HEALTHY SUBJECT AND AN ADRENALECTOMISED WOMAN

METHODS developed recently for the quantitative determination of urinary pregnanetriol [1–5] have proved of value in the investigation of adrenocortical dysfunction. Pregnanetriol (5β-pregnane-3α:17α:20α-triol) is present in the urine of healthy men [6] and women,[2 5] and is excreted in large amounts in the urine of patients with adrenocortical hyperplasia.[1 7 8] It is not certain, however, that the adrenal cortex is the only source of the metabolic precursors of urinary pregnanetriol. Moreover, systematic studies of daily excretion during the menstrual cycle and pregnancy have not been reported.

The present results, which form part of a wider study, give a comparison of the daily excretion of urinary pregnanediol and urinary pregnanetriol in two women with regular ovulatory cycles. The first subject (aged 26) was a healthy volunteer. The second (aged 45) had undergone bilateral total adrenalectomy for Cushing's syndrome 3 years previously. She was in good health, being maintained by prednisone 5 mg. and 9α-fluorohydrocortisone 0·1 mg. daily. Apart from the observation of raised urinary pregnanediol excretion in both cycles, evidence of ovulation was obtained from basal temperature records, urinary œstrogen assays, and vaginal cytology. In the adrenalectomised subject the excretion of urinary neutral 17-ketosteroids and 17-ketogenic steroids fell below the sensitivity of the methods of assay, and this is compatible with the absence of significant secretion from residual or accessory adrenocortical tissue.

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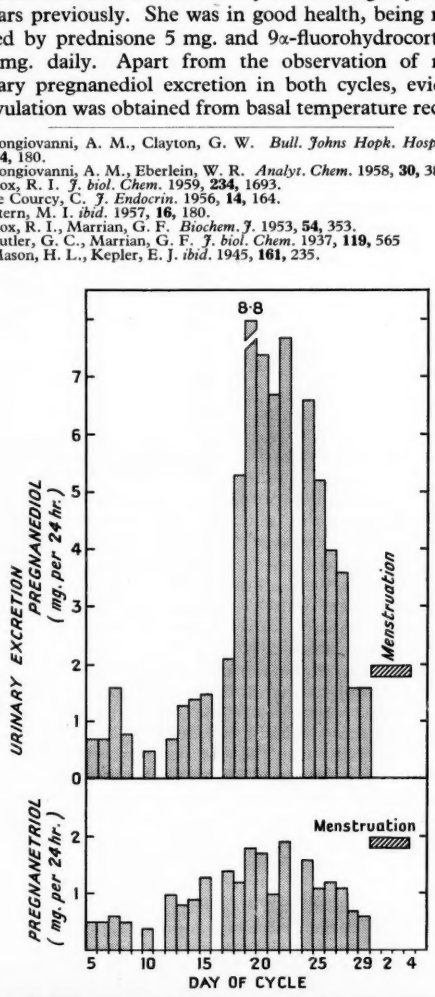

Fig. 1—Healthy subject: urinary pregnanetriol and pregnanediol excretion throughout the menstrual cycle.

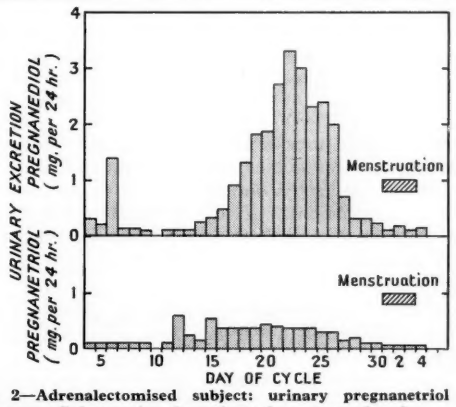
URINARY EXCRETION PREGNANEDIOL (mg. per 24 hr.)
Menstruation
PREGNANETRIOL (mg. per 24 hr.)
Menstruation
5 10 15 20 25 30 2 4
DAY OF CYCLE

Fig. 2—Adrenalectomised subject: urinary pregnanetriol and pregnanediol excretion throughout the menstrual cycle.

METHODS

Urinary pregnanediol and urinary pregnanetriol were determined by the method of Stern [5] (which permits measurement of as little as 0·2 mg. per 24-hour specimen of either steroid). In the adrenalectomised subject the urinary pregnanediol was determined also by the method of Klopper et al.,[9] and evidence for the specificity of the procedure [5] was obtained on days 14 and 21 of the cycle by two further chromatographic procedures, originally developed for the determination of urinary pregnanetriol [4] and plasma pregnanediol.[10] These methods were adapted to permit measurement of either steroid.

RESULTS

Figs. 1 and 2 show the amounts of urinary pregnanetriol and pregnanediol excreted throughout the menstrual cycles of the two subjects.

The first subject (fig. 1) showed a cyclical variation of pregnanetriol excretion, closely following that of pregnanediol, although at a lower level. The excretion of urinary pregnanetriol varied from 0·4 mg. per 24-hour specimen during the follicular phase to 1·9 mg. per 24 hours during the luteal phase. Pregnanediol excretion varied from 0·5 to 8·8 mg. per 24 hours during the same interval.

The adrenalectomised subject (fig. 2) also showed increased pregnanetriol and pregnanediol excretion during the second half of the cycle, although the actual quantities were considerably smaller than in the healthy subject. The urinary pregnanediol values obtained by the two methods agreed well except on day 6 of the cycle, when only 0·1 mg. per 25 hours was found by the method of Klopper et al.[9] A somewhat analogous increase in pregnanediol excretion was seen in the healthy subject on day 7 of the cycle (fig. 1).

We also studied a healthy young woman (aged 18) $2^1/_2$ years after the menarche. As in the case of a young nullipara in another series,[11] only small amounts of

9. Klopper, A. I., Michie, E. A., Brown, J. B. *J. Endocrin.* 1955, **12**, 209.
10. Sommerville, I. F., Deshpande, G. N. *J. clin. Endocrin. Metab.* 1958, **18**, 1223.
11. Brown, J. B., Klopper, A. I., Loraine, J. A. *J. Endocrin.* 1958, **17**, 401.

urinary pregnanediol were excreted. Urinary pregnanetriol excretion was low also, and there was no sustained increase in either steroid during the cycle.

SUMMARY AND CONCLUSIONS

Daily urinary pregnanediol and pregnanetriol determinations in two women showed that pregnanetriol excretion was increased during the menstrual cycle.

The results obtained in an adrenalectomised woman demonstrated a pattern of urinary pregnanediol excretion in the absence of the contribution from the adrenal cortex.

The pattern of urinary pregnanetriol excretion in both subjects suggests the possibility that this steroid may have ovarian as well as adrenocortical precursors.

We are indebted to Dr. P. M. F. Bishop for permission to study the adrenalectomised subject, and to the British Empire Cancer Campaign for financial assistance.

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New Inventions

A PORTABLE FREE-FIELD AUDIOMETER

IT is relatively easy to obtain a pure-tone audiogram from most children who have a mental age of 3 years or above. Sometimes, however, it is impossible to obtain such an audiogram—for instance, if the child is uncooperative or hyperactive. In addition, children under a mental age of 3 years are too immature to be conditioned in the usual play method for obtaining a pure-tone audiogram.

In such cases distracting sounds are produced, observations are made of the responses, and degree of hearing loss, if any, is deduced from such observed responses. It is always wise to try to establish some knowledge of hearing throughout the speech range of frequencies. Responses to complex sounds such as rattles, or even to speech sounds only, show awareness of sounds and not necessarily complete comprehension of sound. The use of pitch bars or pitch pipes has given a better picture than the use of more complex sounds, but these are not always pure tones. To try to obtain a more complete picture a small pure-tone audiometer was built in the Phonetics Department of University College, London, for use in a free field situation.

It is completely enclosed in a box $5^1/_4$ in. $\times 4^3/_4$ in. $\times 5$ in. and weighs $5^1/_4$ lb. It incorporates a loudspeaker and produces pure tones of 500 c/s, 1000 c/s, 2000 c/s, and 4000 c/s. It is calibrated for a distance of 2 ft. and produces intensity levels of 80 db, 60 db, 20 db, and 0 db relative to a normal threshold at each frequency. It is transistorised and battery-operated. There are two switch controls—one for intensity and one for frequency. A press-button switch turns the sound on and off in a smooth fashion as prescribed by the British Standard for Audiometers. Battery strength can be measured. It was calibrated on five normally hearing adults in a silent room. Therefore in a normal room 0 db and 20 db levels will probably not be heard.

When a child is restless and continuously on the move, he can be followed around with the audiometer. When he does settle a distracting sound, using the audiometer, can be made and any response noted. Over a period of time, using different frequencies and intensities a reliable estimate of hearing may be made.

Sometimes children refuse all approaches in a clinical situation, but will respond readily in a home or school situation. This audiometer is so portable that it can be carried anywhere without difficulty.

It has already proved to be extremely useful in many cases where the normal routine assessment was not possible and where the child would not tolerate anything on or close to the ear.

The circuit diagram, with some constructional details, is available from the Phonetics Department, University College, London. A more technical description is to be published in the *Wireless World*.

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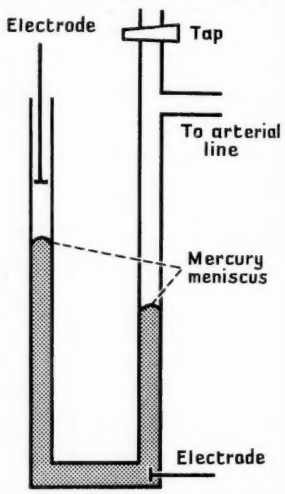
A SIMPLE FLOW-METER AND SAFETY DEVICE FOR THE EXTRACORPOREAL CIRCULATION

MANY varieties of meter, some of them extremely complex, have been used in the laboratory and operating-theatre to measure blood-flow through an extracorporeal circulation. In his review of eight types McMillan [1] makes no mention of the use of line pressure for gauging the rate of flow.

The line carrying blood from pump to patient ends in a cannula inserted into an artery. During perfusion it is customary to measure arterial pressure. If the arterial mean pressure is subtracted from the mean pressure in the line, the resulting value represents the pressure caused by the flow of blood through the cannula at that moment. In the laboratory it is easy to determine the pressure caused by various rates of flow through a cannula, and, in perfusion, to use the pressure value as a measure of flow.[2] For clinical purposes a glass U-tube containing mercury is connected to a branch from the arterial line. By adjusting a screw clip on the branch line, one can measure either pulsatile or mean pressure.



A glass U-tube containing mercury for the measurement of line pressure in an extracorporeal circulation. Excessive pressure arising from obstruction to the line causes the mercury to make contact with an electrode and activate an electrical bell.

In open heart surgery, obstruction of the arterial line or cannula by external pressure, kinking, or displacement is an ever-present hazard. Such obstruction instantly causes a rise in line pressure, and this may be employed to sound a warning signal. The mercury is used as one electrode of an electrical bell system, and the second electrode is placed at a suitable height above the meniscus in the ascending limb of the U-tube (see figure).

The arterial line filter-chamber designed by Dr. D. G. Melrose and manufactured by New Electronics Products Ltd. bears a port to which may be attached a branch line leading to the manometer.

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2. Cleland, W. P., Beard, A. J. W., Bentall, H. H., Bishop, M. B., Braimbridge, M. V., Bromley, L. L., Goodwin, J. F., Hollman, A., Kerr, W. F., Lloyd-Jones, E. B., Melrose, D. G., Telivuo, L. J. *Brit. med. J.* 1958, ii, 1369.

Reviews of Books

The Surgeon and the Child

WILLIS J. POTTS, M.D., surgeon in chief, Children's Memorial Hospital, and professor of pædiatric surgery, Northwestern University Medical School, Chicago. Philadelphia and London. W. B. Saunders. 1959. Pp. 255. 52*s.* 6*d.*

THIS book has been written particularly for obstetricians, pædiatricians, and general practitioners, who are the first to see the newborn child with an anomaly or deformity which requires surgical treatment. A good deal of attention has therefore been paid to diagnosis, so that the need for adequate surgical care can be recognised early enough to be completely effective.

At a time when, in spite of the remarkable progress in the surgery of infancy in the past fifteen years, there are still many who decry the need for special interest in the surgical problems of the newborn, this book can do much good. It is not a standard textbook and does not contain any references to published work, embryology, or details of operative technique, and it reads very well. It does contain the fruits of personal experience as surgeon and surgeon-in-chief at the Children's Memorial Hospital in Chicago, a lot of Dr. Potts' wisdom, many pungent comments, and more good advice than most of the other books about pædiatric surgery put together. It is good to find the "pacifier" or dummy recommended. Not only in Chicago is acute appendicitis less common and less lethal than it used to be; but it is surprising to learn that the 40% incidence there of perforation of the appendix remains unchanged. As one might expect the sections on the anomalies of the heart and great vessels are particularly good, and will provide much useful information to those who, with little experience of these lesions, have to produce a realistic prognosis for parents. This excellent and enjoyable book should be read by all who have to do with infants and children.

Neuropharmacology

Transactions of the Fourth Conference of the Josiah Macy, Jr., Foundation. 1957. Editor: HAROLD A. ABRAHAMSON, M.D., research psychiatrist, the biological laboratory, Cold Spring Harbour; consultant in research psychiatry, State Hospital, Central Islip, New York. New York: Josiah Macy, Jr., Foundation. 1959. Pp. 285. $5.

FROM time to time the Josiah Macy, Jr., Foundation brings together a group of specialists for two or three days to hear and discuss papers on some aspects of recent progress in their specialty. This volume has four articles of interest in experimental psychiatry: clinical studies with taraxein (Robert G. Heath); some relations between chemical structure and physiological action of mescaline and related compounds (Gordon A. Alles); "stop" and "start" systems (John C. Lilly); and the effect of respiratory poisons and anoxia on Siamese fighting fish in relation to LSD-25 reaction (Harold A. Abramson). The speakers were interrupted, cross-questioned and challenged, criticised, and pacified by a group of 25 people for the most part concerned with the nervous system as clinicians, physiologists, or biochemists. Their interpolations are printed more or less verbatim, and add much to the value of the book, which is intended to stimulate critical thinking and new ideas in the scientific analysis of schizophrenia. Because of this, the fact that the conference took place in September, 1957, and was only published this summer is not so important. Any out-of-dateness in the reviews is more than compensated for by the pointed criticisms and the opportunity they give to get to know the qualities of mind of some leading American investigators.

Taraxein is the name given by Heath and his collaborators at Tulane University to a protein they claim to be able to extract from the blood of schizophrenics. Injected into normal volunteers, this protein is said to produce schizophrenic symptoms in them for a few hours, and it can also produce E.E.G. abnormalities in monkeys. It is said to be somewhat like cæruloplasmin, but not extractable from the blood of normal people. Much of the discussion was focused on the choice of subjects for and the conduct of such a clinical trial, to avoid "placebo-reactors" and various effects of suggestion which, seemingly, had not been satisfactorily overcome in this research.

Discussion of mescaline brought with it analysis of the pharmacological action of certain of its close chemical relatives, amphetamine, and adrenaline, and particularly of adrenochrome and adrenolutin, oxidation products of adrenaline which, it has been claimed, are hallucinogenic. The hypothesis that schizophrenia might be due to the abnormal presence of such adrenaline metabolites, however, seems to be dying from lack of observational support. Adrenochrome (like taraxein also, if it exists) is such an unstable quickly disintegrating substance that it is almost impossible to work with it.

"Stop" and "start" systems are areas of the brain in monkeys (and rats) which the animal finds it "pleasant" or "unpleasant" to have stimulated electrically by permanently implanted electrodes. Thus a monkey with an electrode in his caudate nucleus will go on pressing the button which gives him the shock there about three times a second for a 16-hour day, and after 8 hours sleep will start again.

Though this is clearly a book for specialists, it offers a valuable introduction, with references, to the literature on the special themes it discusses.

A History of the Maida Vale Hospital for Nervous Diseases

ANTHONY FEILING, B.A., M.D., F.R.C.P. London: Butterworth. 1959. Pp. 63. 15*s.*

IT was Julius Althaus (1833–1900), a native of Lippe-Detmold and a one-time student in the medical schools of Göttingen, Heidelberg, and Berlin, who in 1866 founded the London Infirmary for Epilepsy and Paralysis, the first premises being at 19, Charles Street (now Blandford Place), Marylebone. Before coming to England Althaus had been privileged to work with Charcot, and doubtless it was from him that he derived his interest in and devotion to neurology, for special hospitals at this time found little support amongst the British public and still less from the profession. Dr. Feiling, who first began his distinguished service to this hospital forty-five years ago, tells of the struggles of the small band of voluntary workers, both laymen and doctors, to establish the highest standards of hospital service in the continual absence of adequate financial resources. It was in the year 1884 that Rickman Godlee brought fame to the little hospital when he removed a subcortical tumour from the brain of a 25-year-old male. Although the patient succumbed to meningitis a month later, this operation was a notable landmark—although not the first craniotomy—in neurosurgery. Like so many other hospitals it now provides on its present site up-to-date amenities in makeshift fashion in premises designed for the simpler needs of over half a century ago.

In a short foreword Sir Ernest Gowers refers to the challenge facing the National Hospitals for Nervous Diseases today and of the altered circumstances brought about by the National Health Service.

Iron Deficiency Anæmia

Report of a Study Group. *World Health Organisation Technical Report Series*, no. 182. 1959. Pp. 15. 1*s.* 9*d.* Obtainable from H.M. Stationery Office, P.O. Box 569, London, S.E.1.

THIS pamphlet points out how serious is the problem of iron-deficiency anæmia in many parts of the world, especially in the tropics; in Mauritius, for example, 50% of certain groups of the population are affected. There is much need for further studies, and a useful table sets out agreed standards of blood values below which anæmia can be considered to exist. The study group set out their ideas on how to determine the prevalence of iron-deficiency anæmia. They review briefly present knowledge of its ætiology, but cite nothing unfamiliar. They point out that a little ferrous sulphate, 1–2 g. daily, can work wonders, and we are glad to see that they agree that

" it is unwise and uneconomical to give as a routine folic acid and vitamin B_{12} to pregnant women ". The recommendations of the group are certainly sound but hardly news to anyone with some knowledge of the literature.

Pregnancy, Birth and Abortion

PAUL H. GEBHARD, WARDELL B. POMEROY, CLYDE E. MARTIN, CORNELIA V. CHRISTENSON, Institute for Sex Research, Indiana University. London: Heinemann Medical Books. 1959. Pp. 282. 30*s*.

IN its two earlier publications, dealing with sexual behaviour in the human male and female, the Institute for Sex Research, founded by the late Dr. Alfred C. Kinsey, said very little about pregnancy. In this third volume, Dr. Gebhard and his colleagues present and discuss their findings in relation to pregnancy and its outcome before and during marriage and in women who were separated, divorced, or widowed. Their method of inquiry enables them to bring forward a great deal of information about the circumstances surrounding conception and abortion. We are left in no doubt, for example, about the social stigma attached to illegitimacy in the United States today. Of 355 conceptions in unmarried girls, 6% resulted in live births, 5% in spontaneous abortion, and 89% in induced abortion. Among the devoutly religious, illegitimacy and induced abortion were notably less common. The available evidence suggests that a premarital pregnancy does not reduce a girl's chances of subsequently marrying. The report refers also to the methods used to induce illegal abortion, and something is said of the cost to the individual concerned.

From their study of abortion in married women, the authors conclude that in the early years of marriage 10% of pregnancies end in spontaneous abortion, but this increases to 20% in late reproductive life. In married women induced abortion is commonest in younger women and in women nearing the menopause. Presumably the younger wives feel that they are not ready to have children and the older women consider that their families are sufficiently large. The material on abortion is well presented and is probably the most important contribution in this book.

In an appendix, short critical accounts are given of the law concerning induced abortion in America, England, Russia, and other countries, and these notes are informative and helpful.

The sample of women studied was severely selected. For the most part, the women were urban dwellers, drawn from the upper socio-economic groups in the north-eastern American states. About a sixth of the women came from three prisons and represent a lower social group. The authors themselves are well aware that their sample does not represent any particular American community. In spite of this reservation, there is much of interest in this well-prepared and carefully presented material for sociologist, obstetrician, and gynæcologist. There is an extensive bibliography, and liberal footnotes give added interest to the text.

The Practical Evaluation of Surgical Heart Disease

The Glover Clinic. Editors: ROBERT G. TROUT, M.D., ROBERT P. GLOVER, M.D. New York and London: McGraw-Hill. 1959. Pp. 132. 77*s*. 6*d*.

ACCORDING to a statement on the flyleaf, this book is " adapted from an American Medical Association Convention exhibit (June, 1957) which was awarded the Billings Gold Medal " and is " an educational publication of the Cardiovascular Research Foundation which will receive all royalties accruing from the sales ". It is a graphic and almost popular presentation of the possibility of investigation and surgical treatment of patients with heart-disease.

The main section consists of descriptions of cardiac defects for which surgical treatment is advised. Each description is in summary form with diagrams of the circulation and the site of the principal auscultatory findings, reproductions of postero-anterior and lateral radiographs and electrocardiograms, and three case-records. The more distinctive auscultatory findings can be reproduced from a gramophone record stored in a pocket inside the back cover. Some of the radiographs, particularly the lateral views, contribute little, partly because of the matt surface on which they are reproduced. Mitral insufficiency is included, because of confidence in the Glover-Davila operation, as a condition in which fair results are to be expected from surgery.

There are short sections, assuming widely varied levels of basic knowledge, on simplified physiology, radiographic interpretation, cardiac catheterisation, and angiocardiography. The seven-page bibliography is almost entirely from the American literature. Type, paper, and binding are excellent. For its original purpose as an exhibit at a medical convention this material is skilfully prepared, but few will be ready to pay a convention fee in order to study a single exhibit.

Trigeminal Neuralgia: Its History and Treatment

BYRON STOOKEY, M.D., professor emeritus of clinical neurological surgery, College of Physicians and Surgeons, Columb a University; JOSEPH RANSOHOFF, M.D., assistant professor of clinical neurological surgery, College of Physicians and Surgeons, Columbia University. Springfield, Ill.: Charles C. Thomas, Oxford: Blackwell Scientific Publications. 1959. Pp. 366. 81*s*.

THE most interesting feature of this monograph is the detailed historical account of the recognition of trigeminal neuralgia and of the development of methods of treatment, attention being properly given to the pioneer work of the two Fothergills, Sir Victor Horsley, and Dr. Wilfred Harris. The clinical account of the disorder is good, but more space might have been devoted to the differential diagnosis of facial pain. The account of operative treatment is detailed and good, but the authors seem unduly pessimistic about the results of alcohol injection and surprisingly give no adequate account of the method of injecting the Gasserian ganglion under radiological control.

Nuclear Explosions and Their Effects (2nd ed. Delhi: Publications Division, Ministry of Information and Broadcasting, Government of India. 1958. Pp. 335. 25*s*. Obtainable from India House, Aldwych, London W.C.2).—A 20-megaton thermonuclear bomb can release the energy of a sizable earthquake or hurricane—energy equal to that of 3 million tons of coal or about 2% of the world's total annual output of electricity. With conventional explosives, it would cost £1000 million to achieve the same power, so the nuclear weapon is by far the cheapest destroyer man has yet devised. In many countries more and more people are becoming fully aware of what these weapons can do and what their testing may involve; and one of the documents that has contributed to their perturbing enlightenment is this comprehensive and relatively unabstruse Indian report, first published in 1956.[1] It is largely the work of Dr. D. S. Kothari of the Indian Defence Science Organisation, with substantial aid from Dr. Homi Bhabha and Dr. V. R. Khanolkar. For this revised edition there was not time to include a full account of the report of the United Nations Scientific Committee on the Effects of Atomic Radiation (published in June last year), but its chief recommendations are given in an appendix. The Indian conclusions on the main issues are in essential agreement with those of the U.N. committee. When Mr. Nehru wrote his foreword last year, Russia had lately suspended nuclear tests, and Britain and the United States had announced their intention to do so. " Let us hope," Mr. Nehru declared, " that this will not be a mere suspension, but a final end to something which threatens the future of humanity."

Malignant Disease University College Hospital, 1946-1950 (Shrewsbury: Wilding. Pp. 631. £5).—A Herculean task has been undertaken by the cancer follow-up department of University College Hospital in publishing as much information as possible about the treatment and follow-up of every case of cancer seen between 1946 and 1950. No attempt has been made to digest or correlate the information presented in rather over 600 tabulated pages, so that there are no results, findings, or conclusions. The work might interest an archivist, but it is doubtful if a clinician would have time or inclination to attempt to work out the significance of this mass of unsifted material.

1. See *Lancet*, 1956, ii, 714.

THE LANCET

LONDON 14 NOVEMBER 1959

Hypophysectomy

DELIBERATE destruction of the pituitary gland in the treatment of metastasising mammary carcinoma was introduced on the ground that certain cancers of the breast were influenced by hormones.[1] The tumour was thought to be stimulated by a combination of hormones comprising growth factor, prolactin, œstrogen, progesterone, and cortisone, with thyroxine as a possible antagonist. Removal of the glands secreting such hormones was calculated to remove the stimulus, arrest the progress of the disease, and even secure regression of metastastic lesions—especially in bones and in skin. In some cases the tumour would eventually become independent of hormone stimulation and would then grow again, but after a delay during which the patient had had a worth-while life free of distressing symptoms. Analogy with operations on the ovaries and the adrenal glands suggested that relapse would follow sooner or later, but whether the remission would be longer after hypophysectomy was uncertain. Although destruction of the pituitary has now been undertaken in many cases, a good deal of doubt still surrounds the operation and its effects.

First, what is meant by hypophysectomy? The capsule of the pituitary gland consists of the fibrous tissue lining the cavernous sinus; and histological sections show nests of cells buried in this fibrous tissue. It has not been seriously suggested that the whole of this dural layer should or could be removed down to every last tag; nor is there any encouragement to believe that the clinical effects depend on the completeness with which the cells lining the capsule are removed or destroyed. There is, for example, variability in the amount of anterior-pituitary cells in and round the stalk of the gland; and pituitary rests may be present in the vicinity, including the nasopharynx. There is, furthermore, no general agreement whether all or any of the tests for complete removal of the pituitary hormones after operation can be correlated with a subsequent remission, or with its degree or duration.

If completeness of destruction of the pituitary were the crucial factor, then the argument for destroying the gland by implantation of radioactive material would be strong in so far as the fibrous capsule was concerned, but not so strong as regards glandular rests in the stalk, nasopharynx, and elsewhere; for these parts cannot be reached by local implantation without damage to the optic nerves and chiasma. Owing to the notorious variability in size and shape of the gland, in the degree to which it protrudes upwards out of the sella turcica, and in its relation to the chiasma, radiographic control is relatively inefficient, except in so far as it guards the operator against damage to the optic pathways and the diaphragma sellæ. That such damage is both possible and dangerous has been repeatedly noted. Sources of gamma radiation in the form of radon seeds have resulted in widespread damage to surrounding structures, including the hypothalamus, but seldom in complete destruction of the hypophysis.[3–5] Radioactive gold, which also emits both beta particles and gamma rays, has been implanted by transnasal routes [6–8]; but, although the gamma radiation is only a fifth of that of radon, the doses required to produce even significant destruction of the pituitary [9–12] endanger the optic chiasma. Yttrium (^{90}Y) as a source of only beta particles has been inserted transnasally [13–15] or transcranially [16] and has been found to be satisfactory: FORREST et al.[3] claim that implantation of two activated sintered rods of ^{90}Y, 6×2 mm., with a total dose of 11 mC regularly produces "virtually complete" destruction. One serious complication which has not been eliminated is rhinorrhœa due to destruction of the diaphragma sellæ; and fatal meningitis has resulted in several cases. These workers suggest that the total dose should be reduced to about 9 mC; and it has also been recommended that the rods be placed more than 2·5 mm. from the diaphragma [17] (though this is a variable structure). Apparently subtotal destruction of the pituitary may be brought about safely by this method, but this has not yet been proved. Checking postmortem material by a few horizontal sections leaves some doubt, as the stalk must be systematically examined. Correlation with late postoperative clinical results has not yet been reported. Prevention of rhinorrhœa following transnasal implantation has been attempted also by tantalum screws,[18] agar powder,[12] and solutions of sodium alginate and calcium chloride.[17] No such danger attends intracranial application of ^{198}Au in fibrin [19 20] or ^{90}Y in wax [21]; but the merits of this in relation to

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those of purely surgical procedures of equal severity in debilitated patients have not been assessed.[7] SMALL [22] claims that regression of metastatic lesions is most complete when, in addition to substantial or subtotal removal of the gland, the stalk is severed, thus separating small remnants from the hypothalamus. In over 100 cases he claims "full recession" of all secondary deposits in 24%. It seems that after hypophysectomy about a third of all cases, or about half of those where the patient survives three months or more,[17] have some remission. Whether remnants of the gland regenerate with or without connection with hypothalamic nuclei is still a matter of guesswork; and what factors, if any, can be correlated with clinical improvement are unknown.

Other conditions which have been treated by hypophysectomy include prostatic carcinoma, Cushing's syndrome,[23–25] malignant exophthalmos, severe diabetes, acromegaly, and malignant melanomatosis. In none of these has the number of cases treated approached that of mammary cancer; and the only additional information to emerge is that melanoma does not seem to depend on hormone stimulation,[26] and that tumours and "hyperactive" cells of the pituitary are more sensitive to radiation than are normal cells of the gland: the hypersecretion of Cushing's syndrome has been corrected, without impairing normal function of the gland, by radon implantation,[27] electrocoagulation,[23] and ^{90}Y.[25]

Certain points seem reasonably clear. Complete hypophysectomy is not yet under discussion, and even "hypophysectomy" might be written in quotation marks. What can be achieved clinically has yet to be correlated with the procedures carried out. One of the principal issues is whether complete destruction of pituitary tissue is either possible or necessary for maximal clinical improvement. Another is whether stalk section is a crucial factor. If either of these is important there is a strong case for intracranial operation at a reasonably early stage when the mortality-rate is low. At present the most nearly complete destruction seems to be achieved by surgical subtotal removal followed by implantation of ^{90}Y into the sella turcica, while only by intracranial operation can the stalk be sectioned. If patients are operated on when they are already completely bedridden or almost moribund the operative mortality-rate is substantially higher. If neither complete destruction nor stalk section is important, then patients can continue to be treated when moribund by intranasal implantation, since the complications of this method are little influenced by the patient's general state. The risk of operative death can then be balanced against the risk of meningitis. Obviously we should know what the surgical aim actually is, but this remains surprisingly recondite.

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Specific Tuberculin Reactions

IN man skin sensitivity elicited by human-type tuberculosis may not invariably be caused by *Mycobacterium tuberculosis*. So far, the strongest evidence for this hypothesis comes from immunological studies [1–5] in which the sizes of reactions produced by tuberculins from different mycobacteria were compared in the same individuals. But the suggestion that non-tuberculous tuberculin sensitivity existed in man preceded the publication of these studies and arose from epidemiological and statistical investigations.[6] Briefly, the evidence consisted of two findings: (1) that in the U.S.A. the proportion of people with negative reactions to a weak dose of tuberculin who react to a strong dose of tuberculin is independent of history of contact with tuberculosis [7]; and (2) that the proportion of people who react to only a strong dose of tuberculin, and the pattern of intensity of the reactions, vary widely between different parts of the world independently of reactions to a weak dose of tuberculin.[7 8] PALMER et al.[9] claimed that almost all the reactions to strong doses (100 tuberculin units [T.U.] of purified protein derivative [P.P.D.]) were not specific for tuberculous infection; and estimates of the prevalence of "non-specific" sensitivity (and, therefore, of the group wrongly classified as tuberculous) were made from this assumption. In London schoolchildren aged 3–16, for instance, the prevalence was said to be 30%.[9] This remarkable claim, which was quite contrary to the generally accepted view in this country of the significance of the tuberculin test has been investigated by the tuberculosis and statistical research units of the Medical Research Council in an investigation which was begun in 1954 and has just been reported.[10]

Tuberculin tests with from 0·3 T.U. to 1000 T.U. of Old Tuberculin (O.T.) were carried out on a large group of R.A.F. recruits, and detailed histories of known contact with tuberculous people were obtained. The findings of PALMER and his colleagues in student nurses in the U.S.A. with 5 and 250 T.U. of P.P.D. were confirmed in the R.A.F. recruits, taking the results with 3 and 100 T.U. of O.T. There was a similar decline in the proportion positive to the low dose of tuberculin from those with histories of close contact to those with no known contact, while the proportion negative to the low dose but positive to the high dose was unrelated to contact. (This finding was the basis of PALMER's hypothesis of the significance of high-dose sensitivity.) The wider range of dilutions used in the M.R.C. study enabled further analyses to be made. These showed that the correlation with known degree of exposure to tuberculosis existed also for 1 T.U., but that those negative to this

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6. Palmer, C. E. *Bull. Un. int. Tuberc*. 1957, **27**, 106, 118.
7. Palmer, C. E. *Amer. Rev. Tuberc*. 1953, **68**, 678.
8. World Health Organisation Tuberculosis Research Office. *Bull. Wld Hlth Org*. 1955, **12**, 63.
9. Palmer, C. E., Nash, E. F. A., Nyboe, J. *Lancet*, 1954, ii, 1274.
10. Pollock, T. M., Sutherland, I., D'Arcy Hart, P. *Tubercle, Lond*. 1959, **40**, 336.

dose but positive to the next higher dose (3 T.U.) showed no such correlation. Therefore, if PALMER's interpretation were to be accepted in Britain, reactions to as small a dose of O.T. as 3 T.U. would be "non-specific" and would not indicate tuberculous infection. This was so difficult to accept that the basis of PALMER's argument was re-examined. He grouped the student nurses according to history of contact with tuberculosis and assumed therefore that they differed in their degree of exposure to infection; and the clear trend of positive reactions to low doses in his three contact groups justifies this assumption. He then assumed that there was the same contrast in degree of exposure to tuberculosis between the residual groups of non-reactors to the low dose of tuberculin as between the reactors. This assumption was not logically valid. Once a group had been selected from each of the original categories of individuals, the remaining categories could not be assumed likewise to differ in their degree of exposure to infection. Another interpretation is more probable—namely, that the test with the low dose, by its very nature, had selected and identified most of those with close or recent exposure to infection, leaving for the high-dose test residual groups which, although differing in contact history, did not differ greatly, if at all, in their degree of exposure. By this interpretation the similarity of the high-dose sensitivity of the residual groups merely reflects the similarity of their past exposure to tuberculosis. By itself, it provides inadequate evidence for the existence, in the countries concerned, of "non-tuberculous" mycobacterial infection associated with reactions to only high doses of tuberculin.

In the M.R.C. investigation geographical variations within Great Britain were also studied. PALMER had found differences between different areas of the U.S.A. in the proportions reacting only to large doses of tuberculin and in the distributions of the reactions by size—"high-dose" sensitivity being more common in the south-eastern States. No regional differences were found, on the other hand, in Great Britain. One finding used to support the hypothesis of "non-tuberculous" sensitivity was the observed patterns of the distributions of reaction size. In Britain a population tested with a dose of tuberculin shows a bimodal curve of reaction sizes, a large proportion having no reaction, very few having small reactions, and some having large reactions. If those not reacting to this dose are tested with a larger dose the pattern is different, there being no "trough", but progressively smaller proportions with increasingly large reactions. The M.R.C. study showed that in Great Britain this difference of pattern was independent of the dose level used. The form of the curve in the residual group is characteristic of a group of subjects from which all those likely to show large reactions to the particular dose of tuberculin have already been removed. The different patterns of sensitivity cannot, therefore, be used as evidence for a non-tuberculous cause of sensitivity to only high doses in this country. In the M.R.C. trial of B.C.G. and vole vaccines 28% of the children were positive to 3 T.U. before vaccination, and 12% were negative to 3 T.U. but positive to 100 T.U.[11] According to PALMER's hypothesis this 12% of children had "non-specific" reactions and were uninfected by tubercle bacilli. But in 1957 the corresponding proportions were 8% and 24%[12]; and on PALMER's hypothesis tuberculous infection had decreased but non-tuberculous infection had substantially increased. This interpretation is unreasonably complex. It seems much more probable that the differences are entirely accounted for by decrease in both the frequency and the intensity of exposure to infection in childhood.

The report of the M.R.C. investigation concludes that nothing in the findings makes it necessary to postulate that any agent other than *Myco. tuberculosis* is responsible for the weak, or even the very weak, sensitivities to tuberculin in Great Britain. Infection by non-tuberculous mycobacteria does occur in this country, and sensitivity to tuberculins from mycobacteria other than *Myco. tuberculosis* probably exists; but there is no reason to suppose that this is common, and the epidemiological and statistical approach is inadequate to demonstrate it. Certainly for practical clinical purposes in this country it may be accepted that, in the absence of previous B.C.G. vaccination, sensitivity to only 100 T.U. implies tuberculous infection.

The hypothesis that non-tuberculous tuberculin sensitivity occurs in man is now seen to have been based in part on invalid arguments. It has led, however, to a much more rational line of investigation, initiated by PALMER himself, through immunological studies using tuberculins from different mycobacteria.[13] With these studies it should be possible to establish the extent of non-tuberculous mycobacterial sensitivity in man and, in conjunction with bacteriological investigations of the so-called "atypical mycobacteria", the organisms causing it. In Britain such sensitisation is likely to prove infrequent and unimportant; but, as we pointed out in 1954,[14] the position may be very different elsewhere in the Commonwealth.

Emergency Obstetric Anæsthesia

THE dangers associated with general anæsthesia for emergency obstetric procedures have attracted much attention in the past few years [15–17] and few can now be unaware of the small, but significant, number of maternal deaths due to inhalation of vomit. The maternal death-rate directly attributable to anæsthesia has been estimated as about 0·2 per 1000 operative deliveries.[18] As a result there has been a pronounced swing in favour of local analgesic techniques, such as pudendal-nerve block, whenever the patient and the obstetric operation can be dealt with by these means. Local analgesia, which can probably be used for as many as 60% of all forceps deliveries,[15] is particularly useful in domiciliary practice, where the doctor is often single-handed and is likely to

11. Medical Research Council. *Brit. med. J.* 1956, i, 413.
12. Medical Research Council. *ibid.* 1958, i, 79.
13. *Lancet*, 1959, i, 456.
14. *ibid.* 1954, i, 244.
15. Parker, R. B. *Brit. med. J.* 1956, ii, 16.
16. *Rep. publ. Hlth med. Subj., Lond.* 1957, no. 97.
17. *Lancet*, 1955, i, 956.
18. Morris, W. I. C See *Brit. med. J.* Sept. 5, 1959, p. 361.

be dealing with less complicated obstetrical procedures than in a hospital department. The efficacy of local analgesia can be enhanced by self-administered inhalational analgesia—trichloroethylene is best for this purpose. Intravenous administration of a mixture of pethidine, a narcotic antagonist, and a phenothiazine derivative has been recommended for the same purpose; but, though such a combination can quickly produce both effective analgesia and docility—indeed, some workers recommend it under the title " ataralgesia " or " hypoanæsthesia " instead of either local analgesia or full general anæsthesia [19 20]—it is less controllable and potentially more dangerous than a simple inhalational method.

General-anæsthetic sequences, other than the traditional ones based on chloroform or ether, have also been investigated for emergency obstetric operations in an attempt to discover a safe method when local analgesia is impracticable. The use of a cuffed endotracheal tube with muscle relaxant drugs has been advocated, not only to decrease the risk of pulmonary aspiration, but also to limit the amount of general anæsthetic needed and thus to offset the chances of fœtal depression.[21] The risks associated with this technique arise during the induction; for, once the tube lies in the trachea with the cuff blown up, the anæsthetist has control of the patient's airway. Methods of quickly procuring this control necessitate paralysis of respiration, and have hazards of their own which an inexpert anæsthetist may fail to circumvent.

The belief that purely inhalational anæsthesia is safe is based on the supposition that vomiting, should it occur during induction, will be accompanied by reflex glottic closure; hence pulmonary aspiration is unlikely, particularly if the patient is maintained in a slight head-down tilt or preferably in the lateral position. In practice, however, the danger is greatest during the operative procedure, when the obstetrician's manipulations may lead to reflux from the œsophagus or stomach, or, if the patient is too lightly anæsthetised, to vomiting. In either event, pulmonary aspiration is likely since glottic reflex activity is somewhat depressed at this stage, and the hazard is accentuated if the patient is in the lithotomy position.

Too little attention has been devoted to the effects of general anæsthesia on the fœtus, particularly when it is already at risk for obstetrical reasons. HODGES et al.[22] believe that deeper inhalational anæsthesia than that provided by nitrous oxide alone with an adequate concentration of oxygen is likely to increase the risk of fœtal distress. In a survey of 264 women who underwent cæsarean section, manipulation and mid-cavity forceps delivery, or outlet forceps delivery, they compared the effects of different sequences of anæsthesia and found that the proportion of infants fully active within sixty seconds of delivery was 43% when nitrous oxide, oxygen, and ether were given, but 64% following a small induction dose of thiopentone, paralysis with suxamethonium, intubation, and maintenance with nitrous oxide and oxygen by controlled respiration. The many variables in this small series preclude a final conclusion, but the results accord substantially with those of other investigators and suggest that even small amounts of potent inhalational agents such as ether, cyclopropane, or trichloroethylene may materially affect the fœtus.

Do the older and well-tried methods of general anæsthesia commonly used for emergency obstetric operations in the labour ward give results for the mother and the child that match those of the more modern techniques that are nowadays generally used in the operating-theatre? No firm answer is yet possible, though on balance the evidence seems to favour the newer techniques; but, as HODGES et al. remark, with advances in technique the potential dangers of inexperience increase. No less important than the technique is the doctor giving the anæsthetic; and consequently an attempt—so far not completely successful—is being made to ensure that, when general anæsthesia is necessary, it is administered by an experienced anæsthetist.

19. Hayward-Butt, J. T. *Lancet*, 1957, ii, 972.
20. Crawford, J. S. *Brit. med. Bull.* 1958, **14**, 34.
21. Coleman, D. J., Day, B. L. *Lancet*, 1956, i, 708.
22. Hodges, R. J. H., Bennett, J. R., Tunstall, M. E., Knight, R. F. *Brit. J. Anæsth.* 1959, **31**, 152.

Annotations

NOMENCLATURE OF DEGENERATIVE HEART-DISEASE

THE immense amount of investigation that is being carried out on degenerative heart-disease seems at times to be in danger of becoming confused by inconsistencies in the use of diagnostic terms. The International Classification of Diseases lists under categories 420, 421, and 422 a large number of conditions as arteriosclerotic and degenerative heart-disease. Many of these, such as atheroma, arteriosclerosis, myocardial infarction, and coronary thrombosis, are essentially degenerative processes, which can be identified with certainty only by the pathologist at the postmortem table. The clinician at the bedside can only assert the presence of *ischæmic heart-disease*, though he may often be able to give a good opinion as to the probable pathological cause. The majority of epidemiological and experimental studies on possible causal factors of degenerative heart-disease are based either on records of death certificates, usually signed without a necropsy, or on bedside diagnosis. In these circumstances a pathological diagnosis is not justified, and it is safest to describe the condition as ischæmic heart-disease.

The use of morbid-anatomical diagnoses, when there is no certainty of their accuracy, may lead to loose thinking and wrong conclusions about ætiology. Atheroma, arteriosclerosis, and major coronary thrombosis are three separate processes. To consider them as one disease, as is done implicitly in many papers, must lead to confusion. Atheroma is primarily a disorder of the intima of the vessels, whereas arteriosclerosis arises in the media. Commonly in laboratory animals, less usually in man, extensive atheroma is present with little or no arteriosclerosis. Conversely in man there may be extensive arteriosclerosis with little atheroma. It is true that the two conditions are closely associated and often are found together, but the use of the portmanteau word " atherosclerosis ", which is now so common, seems

undesirable in that it suggests the presence of a single disease. Similarly myocardial infarction may arise without thrombosis, or indeed without complete obstruction of a coronary artery.

These distinctions are well known to doctors from their training in the postmortem room. But nowadays much of the research on degenerative heart-disease lies in the hands of chemists and statisticians, who cannot automatically be assumed to appreciate these differences. In endeavours involving cooperation between different scientific disciplines, care in ensuring the accurate use of technical terms is especially necessary.

MOTHERS AND FATHERS

IN 1939 Faris and Dunham [1] found that schizophrenia was commoner in the poor areas of Chicago, near the industrial and business centres, than in other districts of the city. Studies in other towns, especially large towns, and other countries have confirmed this observation. Most of the important questions which it raised have yet to be answered, but last week at the Maudsley Hospital, Dr. J. A. Clausen described a useful contribution.

For some years Dr. Clausen and the National Institute of Mental Health at Bethesda have been inquiring into the social background and early life of psychiatric patients. Their first study was into the childhood and upbringing of all schizophrenics treated in Maryland hospitals over a twelve-year period. Compared with normal controls, more of the pre-schizophrenics were isolated in childhood, but close examination of the data showed that this could be the result rather than the cause of their condition. Another difference was that the patients, though not necessarily the other children in the family, recalled their mothers as the dominating figure and their father as a relative weakling. This finding was especially common in middle-class families, and was less usual in the larger group of poorer patients. Dr. Clausen and his associate, Dr. M. L. Kohn, are now examining the family pattern in 200 middle-class and 200 working-class homes.

Interviews with different family members on such subjects as parental dominance, peer relationships, restrictiveness, and discipline are still being analysed, but some interesting facts have already emerged. Thus the working-class try to instil in their children qualities, such as honesty and cleanliness, which the middle-class are apt to take for granted. The middle-class are more concerned that their child should show energy and initiative and develop his talents and personality. About 80% of mothers, fathers, and children agreed that the mother handled day-to-day decisions but that the parents usually decided big things together. For major family decisions if one parent took sole responsibility, it was more often father. This image of the authoritative father was clearer among the children (especially among sons) than the parents. The mothers saw themselves as mildly dominant in decisions about the children; the fathers thought they were overwhelmingly so, especially in decisions about daughters. Mothers who regarded themselves as the less dominant parent said that when angry they " held themselves in " and gave way in a dispute. Mothers who admitted that they lost their tempers easily were more often seen as highly dominant by their husbands —even those who did not see themselves as authoritative figures. Irrespective of maternal dominance, a warmer father/son relation was found in middle-class families. In the working-class the dominant mother was far more likely to disparage the father and call attention to his inadequacies. Working-class family relations, indeed, seemed more full of problems, though these did not necessarily later cause mental illness.

Dr. Clausen hopes in the next stage of his investigation to arrange for an observer to join families temporarily to see what really goes on, and a start has been made with nursery-school children. Family attitudes and practices have yet to be correlated with psychopathology, but careful on-the-spot studies of this kind will offer child psychiatry and social psychiatry some of the objective standards and information which they still lack.

1. Faris, R. E. L., Dunham, H. W. Mental Disorders in Urban Areas. Chicago, 1939.

RESPIRATORY PARALYSIS AFTER URETEROSIGMOIDOSTOMY

MUCH interest has been aroused by the blood-electrolyte changes which may follow surgical diversion of urine into the bowel. Reabsorption of electrolytes from urine retained in the intestine, coupled with impaired renal function, may bring about a state of chemical imbalance usually characterised by a rise in the serum-chloride and a fall in the alkali reserve. While " hyperchloræmic acidosis " has now become well recognised as an occasional sequel of ureterocolic anastomosis, an incidental loss of potassium—possibly influenced by other factors—has attracted somewhat less attention.

Hypokalæmia has, however, been reported in about a third of all patients submitted to this operation,[1] and serious symptoms have sometimes arisen. Among these, anorexia, vomiting, progressive weakness, and diarrhœa have been prominent—the diarrhœa probably aggravating the potassium loss. Similar symptoms have been noted in cases of vesicointestinal fistula, where potassium depletion has been associated with protracted urinary diarrhœa. Conversely the full hypokalæmic syndrome may be induced in susceptible patients already suffering from anorexia (but without diarrhœa) merely through reduction of potassium intake. In a study of seven cases Lowe, Stowers, and Walker [2] draw attention to the variety of electrolytic disturbances which may follow ureterosigmoidostomy and emphasise the need for careful biochemical assessment and prophylaxis of ascending renal infection. Steinbeck and Tyrer [3] comment on the occurence of hypokalæmic pareses and cite a case in which there were recurrent attacks of quadriplegia and respiratory embarrassment. In such cases the rapid and apparently unexplained onset of severe asthenia and malaise may give rise to difficulty in diagnosis. Straffon and Coppridge [4] have reported two cases in which extensive muscular weakness progressing to respiratory paralysis invited a differential diagnosis of acute neurological disease. In one case a girl of 12, who had undergone ureterosigmoidostomy six years previously on account of vesical exstrophy, was admitted with a tentative diagnosis of poliomyelitis after three days of progressive muscular weakness of the legs and back. In the other—a man of 56 who had undergone ureterocolic anastomosis fourteen years previously—a rapidly spreading flaccid paralysis simulated Landry's acute ascending myelitis. Both patients required temporary resuscitation in a mechanical respirator pending detection of the electrolyte deficiency, and both later responded dramatically to potassium replacement therapy.

1. Jacobs, A., Stirling, W. B. *Brit. J. Urol.* 1952, **24**, 259.
2. Lowe, K. G., Stowers, J. M., Walker, W. F. *Scot. med. J.* 1959, **4**, 473.
3. Steinbeck, A. W., Tyrer, J. H. *Brit. J. Urol.* 1959, **31**, 280.
4. Straffon, R. A., Coppridge, A. J. *J. Amer. med Ass.* 1959, **171**, 139.

DOCTOR IN THE BOX

"WHICH of the many injuries sustained by the claimant caused chronic alcoholism: answer Yes or No?" Thus may run the doctor's nightmare before his appearance in court in a case in which he has, wittingly or otherwise, become involved in a professional respect; for there are few who view such a public ordeal with complete equanimity. In British courts, the evidence on fact and opinion elicited by counsel's questions in the examination-in-chief is open to be tested by cross-examination, when a witness may be questioned closely and persistently. Once in the witness-box the doctor is, therefore, likely to find that a straightforward examination-in-chief will be followed by questions which will require knowledge and rapid but careful thought if helpful and clear answers are to be given. And all this in public, with the full attention of the court and Press, so that incautious remarks are apt to resound far more than similar remarks made in the seclusion of the consulting-room. The doctor's peace of mind may be further disturbed by the sight of a steady succession of notes being passed to cross-examining counsel by the medical adviser for that side, making it quite clear that any deficiencies of medical knowledge on the part of the lawyer are constantly being made good.

Merliss et al.[1] emphasise how important it is to keep complete and detailed records, so that, if litigation arises, reliable reference may be made to the documents. Abbreviations in records are a hazard, unless their use can really be justified, for counsel are not slow to seize upon possible ambiguities or any other apparent defects in case-records, sometimes using them with devastating effect in cross-examination.

Bias and sympathy on the doctor's part may easily lead to an impulsive and rash opinion, and if lawyers proceed on the assumption that that opinion is correct then the doctor may find himself in court unhappily learning that the objects of cross-examination include the destruction of his assertions and the strengthening of the opinions of the other side, while someone, more unhappily still, faces an adverse verdict and costs. This kind of disaster can usually be averted if no opinion is ever given without deliberation and reference to authoritative literature. At no time should a doctor be drawn into professing an opinion to lawyers on the understanding, expressed or implied, that he will not at any time be called to the witness-box to give evidence: either the opinion is to be regarded as worthy of repetition and test in court, or it should not be given at all.

In the court with the heaviest demands on doctors' time, the coroner's court, there is no cross-examination, but the coroner's questions may be followed by counsel's, often designed to lay emphasis in some special direction, and these additional questions can be as probing and as difficult as any in a thoroughgoing cross-examination in other courts. Quite often the most junior member of a hospital clinical team is sent to the coroner's court to give evidence, even though his comprehension of the case may be imperfect, and it is scarcely surprising that this can result in counsel's questions not always being answered with the clarity, accuracy, or determination of which a senior clinician might have been capable.

The worth of medical evidence elicited by cross-examination is often questioned after the hearing of a sensational case in court, when both doctors and the general public express doubts about the merits or even relevance of statements given during what is a stressful ordeal. From time to time suggestions [2] are made to the general effect that it would be an advance if conflicting medical evidence were to be heard and assessed by a panel of experts, or else that expert witnesses should be examined by the judge rather than by opposing counsel.

The expert panel could well be a time-saving device and a guarantee that the evidence given at a trial is genuine and truly expert; but it is sufficiently far from established British practice to cause uneasiness about defeating the object of allowing justice to be seen to be done. It might be safer to continue to hear all the evidence in court and put it to a judge or a jury in such a way that they could form their own opinions of the whole matter, for they, after all, are the final arbiters. If the testifying doctor gives an honest and sincere opinion, and if he is prepared to support his views with reasonable references to textbooks and articles, then he will not be likely to confuse the court or to run into serious difficulties in the cross-examination.

One thing is certain—a doctor should not withhold useful evidence just because he is afraid of having a bad time in court. As Merliss et al. remark, "Cross-examination is a rigorous test for any doctor to undergo. Yet, unless he is willing, and unless he delivers testimony effectively, he fails in an important service to his community and to his patient"

THE SALIVA IN DEPRESSION

THE need for some objective measure of mood-change is clear enough: clinical detection of the suicidal risk is a baffling problem. Depression, at times, is a normal condition if not too severe or long-continued; and much of the recent symposium on this subject [3] was taken up with questioning as to what was meant by the word. Over twenty years ago Strongin and Hinsie [4] observed that, while the salivary excretion-rate in schizophrenia is somewhat higher than normal, it is greatly reduced in depression. Peck [5] has replaced the cumbersome technique with a suction cup over the parotid duct by a more practicable one in which standard dental rolls of cotton-wool are weighed after lying for two minutes over the duct orifices. This procedure has become known as the S.H.P. (or Strongin-Hinsie-Peck) test, and the results with it are interesting.

Clearly significant differences beyond the 0·01 level were found between normals and depressives, irrespective of sex, age, and race; but among those under 19 years of age this difference became lost in a generally higher level of secretion, and Negroes gave relatively higher readings in both normal and depressive groups. Body-weight and smoking habits did not seem to interfere with the results; but gum-chewing did, and intercurrent fever lowered the readings. In some a diurnal fluctuation was noted, with greater secretion in the evening; and Peck suggests a possible relation to the well-known diurnal changes of mood. As he observes, the overlap between the normal and depressed subjects is such that no cut-off point can be identified, and much remains to be done before this test can be usefully used for diagnosis. Psychosomatic accompaniments to depressive illnesses have long been observed,[6] but their measurement has not, hitherto, been very helpful clinically.

1. Merliss, R. R., Gelfand, L., Magana, R. *New Engl. J. Med.* 1959, **261**, 175.
2. See *Lancet*, 1956, i, 427.
3. See *ibid.*, Oct. 3, 1959, p. 509.
4. Strongin, E. I., Hinsie, L. E. *Amer. J. Psychiat.* 1938, **94**, 1459.
5. Peck, R. E. *A.M.A. Arch. gen. Psychiat.* 1959, **1**, 35.
6. See, e.g., Cleghorn, R. A., Curtis, G. C. *Canad. psychiat. Ass. J.* 1959, **4**, suppl. (McGill University Conference on Depression and Allied States); p. S13.

Special Articles

STRESS AS A FACTOR IN DISEASE *

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A GREAT deal is heard about psychological stress as a cause of disease. The stress suffered by the top business executive and his supposed consequent increased liability to ischæmic heart-disease is a recurrent popular theme which does not seem to be supported by the present evidence.

Consideration of stress as a factor in disease is complicated by two inadequacies—of definition and of measurement. Rees (1959) outlined the changes in the meaning of the word " stress " over the years and pointed out that in medicine today it is used to mean the external force applied to the organism, the internal resistance by the organism to the external force or, as Selye defines it, a specific syndrome occurring in the body in response to certain stressors. A further difficulty is the use of " strain " as synonymous with " stress ", especially in discussing psychological situations. The *Oxford Dictionary* confirms that these words, as used today, are practically interchangeable. Their meaning can be clarified by using them in a sense similar to that in which they are used in physics. Stress can then be defined as " the external stimulus producing or tending to produce disturbance in the organism " and strain as " the disturbance produced within the organism by the external stress ".

There is no difficulty in accepting that physical stress, in the sense of external physical stimulus, is a factor in the ætiology of disease. There is ample evidence that external influences such as trauma, infection, starvation, air pollution, contact with toxic substances at work, and smoking are harmful under certain circumstances. Because the causal relation between physical stress and disease is clear, it is sometimes assumed that mental stress must also be a factor in disease. The evidence for this is much less clear.

One reason why the evidence that mental stress produces disease is much less convincing than it is for physical stress is because mental stress is so difficult to measure. Each of us is faced with a multitude of potentially stressful psychological situations throughout our lives. Because of this it is difficult to define groups of people all of whom are subjected to similar mental stress, and in whom the resultant strains can be measured and compared with other groups subjected to different stresses. But if a large group of people are doing identical work and come from the same social environment, then it may reasonably be supposed that the stresses endured by each of them in his home and social life are so diverse that, for the group as a whole, they cancel each other out. If this group is compared with another group coming from a similar social environment but doing a very different type of work, then any evidence of strain in one group would, theoretically, be due to the different stresses in the two occupations. The only measurable indices of the resultant strains, if any, which are available under these circumstances, are the incidence of death or of sickness absence attributed to various illnesses in the groups being compared. If the incidence of these illnesses varies in groups subjected to different occupational stresses, then a working hypothesis is that, because other factors are apparently neutralised, these occupational stresses were factors in producing these diseases. If no such effect is found, then the stresses of such occupations are not sufficient to cause significant amounts of disease in the groups, or there is no evidence that stress causes disease or some other factor, or factors, have been introduced which are masking the effects of stress.

* A paper read to the county district group of the Society of Medical Officers of Health on July 11, 1959.

The Data

In this paper data of two types are examined to see what epidemiological evidence there is for stress being a factor in disease. Throughout stress is taken to mean " external psychological stimuli due to occupation tending to produce disturbance in the organism ". The data used are those for mortality from coronary-artery heart-disease in London's bus drivers and male conductors and in other occupational groups, and the sickness-absence experience of four groups of London Transport employees, with special reference to sickness absence attributed to functional nervous disorders and to diseases of the stomach and duodenum.

There are many difficulties in using industrial sickness-absence records for epidemiological studies. In *Health in Industry* (1956) London Transport published a great many data about the sickness-absence experience of employees in several different occupations, in which bias in the method of collection and presentation of the data was eliminated, and in which there was evidence that the accuracy of medical certification did not invalidate comparison of experience between the occupational groups. One important variable remains in the data—the effect of selection on their composition. There is the effect of self-selection by the individual choosing to do a certain job, the effect of selection by management in deciding that the individual is physically, mentally, and by occupational and educational experience suitable to do the job chosen, the continuing effect of selection by employee and employer in remaining in the job, and the effect of selection by employee or employer in leaving the job. Some of these effects are apparent in the data and can be allowed for or even turned to advantage. Other effects are unpredictable and some deductions from the material must be accepted with caution.

CORONARY-HEART DISEASE

In the first study of the coronary-heart disease experience of London Transport's drivers and male conductors (as measured by the first clinical episode), Morris et al. (1953) showed that conductors had less coronary-heart disease than drivers. They also showed that the disease appeared in the conductors at a later age and in a less severe form than in the drivers.

The age-standardised rates of incidence of the disease for men aged 35–64 years was 2·0 per thousand for the conductors and 2·7 per thousand for the drivers; 38% of the episodes in the conductors presented as angina pectoris compared with only 13% in the drivers. When the cumulative mortality from the first clinical episode was studied, the experience of the conductors was clearly better than that of the drivers; the cumulative mortality-rates for the conductors at the end of the first three days, first three months, and first three years were, in each case, half of those for the drivers.

These bus drivers and male bus conductors came from similar social groups; they all lived in London but not in one area, because they generally lived near their places of work which were well spread over London; their hours of work were the same, though highly variable week by week for individuals; their rates of pay were very similar; they had the same health and welfare services; they had the same conditions of sickness absence and sickness benefit and there is no reason to suppose that, when they were ill, there was any difference in the standard of medical diagnosis or of death certification applied to them. The one respect in which they differed most was in

the work which they did. For these reasons bus drvers and conductors were two very useful occupational groups to compare epidemiologically.

In seeking for explanations for the differences in the incidence of and mortality from coronary heart-disease between these two groups of men, Morris et al. (1953) suggested three possibilities. These were that the greater physical activity of conducting compared with driving protected the conductors from the severe manifestations of the disease; that there were differences in the constitutions of drivers and conductors (that is, that different types of men selected themselves for these very different jobs); and that, though there were mental " stresses " in both occupations, they were of such different kinds as to explain the lower incidence in the conductors.

Physical Activity of Work

Much evidence has been presented in this country and Europe, though less in the United States, that, when the coronary heart-disease experience of different occupational groups was examined, those men who were employed in jobs involving little physical activity had a worse experience than those whose work involved much physical activity.

Telephonists and clerks in the Post Office had a worse experience than postmen, and, when the Registrar General's occupational mortality-rates for coronary heart-disease were classified into those for physically heavy jobs, intermediate and doubtful jobs, and physically light jobs, the mortality-rates for men in physically active jobs were lower than for those in intermediate jobs, which in turn were lower than for those in physically light jobs. Recently Morris and Crawford (1958) have shown, in a nationwide necropsy survey, that post-mortem findings tell a similar story. Among men who had died from some other cause than coronary heart-disease, those who had been employed in physically light occupations had more ischæmic myocardial fibrosis and large healed infarcts than those in active occupations who, in turn, had more than those employed in heavy occupations.

The accumulating evidence seems to indicate that physical activity of work, by some mechanism not yet understood, protects middle-aged men to some extent from coronary heart-disease. Differences in the amount of physical activity at work is one possible explanation of the observed differences in the incidence of the disease in bus drivers and conductors.

Constitution

There is some evidence that body-shape is related to the development of coronary heart-disease (Gertler and White 1954). Square, muscular men, particularly if tending to fat, are said to be particularly prone.

Morris, Heady, and Raffle (1956) compared the sizes of uniform of samples of London Transport bus drivers with those of male conductors. It was shown that at all ages—even in the 25–29 age-group, before occupation was likely to have caused the difference (there are no bus drivers under the age of 24 in London Transport)—there were much higher percentages of drivers than conductors with trouser waist-measurements of more than 38 in. and jacket breast-measurements of more than 40 in., after due allowance had been made for variations in height.

These differences in the uniform sizes of drivers and conductors may be the result of the interaction of at least two factors—selection and occupation. The " rounder " men tended to select themselves into the less active job—driving—which in itself predisposed to increasing obesity.

The coronary heart-disease mortality experience of London's busmen has now been studied for ten years (1949–58), and enough material has been collected to analyse the data by occupation, by two broad age-groups, and, as a measure of physique, by three trouser waist-measurements (Morris, Heady, and Raffle 1959). As would be expected, the older (50–64) conductors had a much worse experience than the younger (35–49) conductors, and the older drivers than the younger drivers. The conductors in each age-group had a better experience than the drivers, confirming previous findings. These two trends, with age and occupation, were consistent within each of the three trouser waist-measurement groups—i.e., fat young drivers had more sudden deaths from coronary heart-disease than fat young conductors, thin young drivers than thin young conductors, and middling-size drivers than middling-size conductors.

Evidence seems to be accumulating that the difference in coronary heart-disease experience between these two occupational groups was in some way related to the difference in constitution between the groups—how is not yet known.

Stress

Stress is often said to be a cause of coronary heart-disease. The Registrar General's social-class mortality figures are sometimes quoted in support of this, with the implication that in the managerial and professional occupations included in social class I stress is the explanation for the high rates for the disease. Morris (1959) showed that the descending rates of incidence of coronary heart-disease with descending social class could be largely explained by the increasing number of men in occupations involving physical activity which are included in each successive lower class.

When occupations were classified into those involving light, active, and heavy work, there was no trend apart from physical activity of job at 45–54, and at 55–64 this was important only in heavy workers. Morris and Crawford (1958) further showed, in their necropsy survey, that the expected trend with social class of the frequency of ischæmic myocardial fibrosis, in men dying of other conditions than coronary heart-disease, disappeared when the social classes were broken down into categories of physical activity. Light workers in each social class had a similar prevalence of ischæmic scarring.

There was no social-class trend for coronary heart-disease in married women under 65 (Logan 1959), so it seems unlikely that differences in housing and diet between all the classes were major factors in the trend in men. In any case, field surveys do not show any obvious variation in diet between the social classes in this country. At present stress cannot be excluded as a contributory factor in the social-class mortality-rates, but there is no direct evidence for its inclusion.

It would be easy to accept the theory that the different types of stress in bus driving and conducting, as well as physical activity and constitution, are factors in the different experience of coronary heart-disease in the two groups. But, as Morris et al. (1953) pointed out, this means accepting such a close association between the psychological factor of stress and the physical factor of physical activity that, however the data for busmen or other occupational groups were analysed from the physical point of view, the unknown psychological factors also intervened. The possibility that constitution is a second factor strengthens this argument. This would now entail accepting that, whenever the physical factors of activity and constitution were shown to be operating, the unknown psychological factors were also present. This is difficult to credit but it is not impossible, because the individuals' reaction to stress, which is part of their personality, could be linked with that part of their personality which leads them to prefer an active or an inactive job. This facet of personality could be associated with a particular type

of bodily configuration—in other words, both could be genetically determined. There is no evidence to support such speculations, and there is no epidemiological evidence yet that stress is a factor in coronary heart-disease.

OCCUPATIONAL SICKNESS-ABSENCE STATISTICS

Occupational sickness-absence statistics are another source of information which can be used in examining the possible role of stress (as here defined) in the production of disease.

Four occupational groups in London Transport have been chosen for study here. The data have been taken from *Health in Industry* (1956). They are the Central Bus (red) drivers and male conductors, the workshop staff at the main overhaul works at Chiswick, and the motormen (train drivers) and guards on the Underground. As I have already pointed out, drivers and conductors have so many common features in their modes of life that they are useful groups to study epidemiologically. The workshop staff and the motormen and guards also have so many common features with each other, and with the drivers and conductors, that many of the variables have been matched which make industrial sickness-absence statistics difficult to use for epidemiological investigations. In fact, apart from the actual work which they did, the one major point

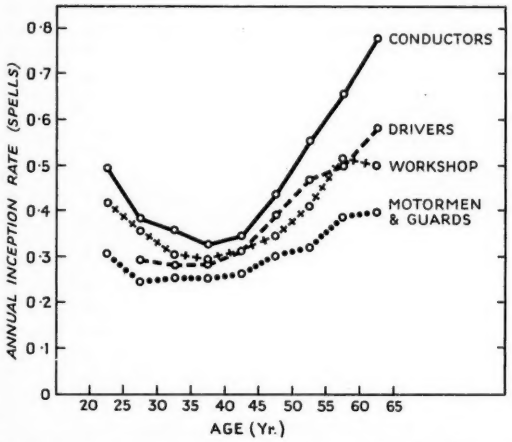

Fig. 1—Average annual frequency of sickness absence for all causes 1949–52 (absences of 4 days or more).

of dissimilarity between the four groups was that the workshop staff did not work rotating shifts, whereas the other three groups did.

Sickness-absence from All Causes

Taking the average number of spells of absence per man per year for all causes (including accidents) in five-year age-groups, for each of the four groups of staff for the years 1949–52 (1950–52 for motormen and guards), there was little difference between all the groups in the middle working years of 30–45, but there were differences at the younger ages and, especially, at the older ages (fig. 1).

The differences were apparent throughout the working years and were consistent with the theory that conductors had to feel physically fitter, and were, therefore, more likely than the drivers and the workshop staff to have spells of certified sickness-absence. The latter had much the same experience as the drivers throughout. The motormen and guards were less handicapped by sickness from going to work than the other groups. (The difference between the groups is likely to be real because the man-years of experience for each of the four groups were 48,000 for conductors, 56,000 for drivers, 16,000 for workshop staff, and 11,000 for motormen and guards.)

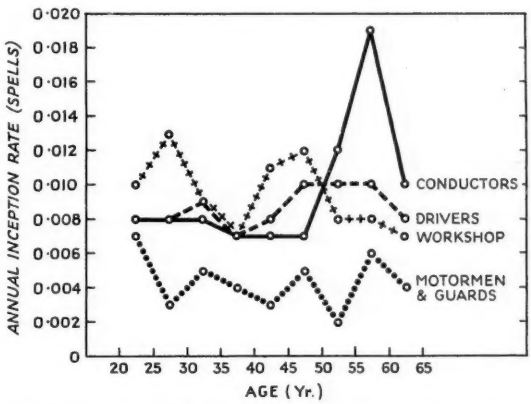

Fig. 2—Average annual frequency of sickness absence for functional nervous disorders 1949–52 (absence of 4 days or more).

When the data were classified into broad groups of diagnoses, the conductors tended to have more spells of sickness-absence than the drivers in each of twenty broad diagnostic groups. (The composition of the twenty broad diagnostic groups was given in *Health in Industry* [1956] and was based on the 3-figure coding of the International Statistical Classification of Diseases, Injuries and Causes of Death [1948].) This even applied to diseases of the circulatory system where the excess of coronary heart-disease in drivers was overshadowed by the excess in conductors of other disease in this group. It can, therefore, be said at this stage that if stress were a very important factor in the production of common diseases, then the data would suggest that the occupation of bus-conducting is more "stressful" than that of bus-driving, being a motorman (train driver) or a guard on the Underground, or working in a light-engineering factory.

Functional nervous disorders and diseases of the stomach, two of the broad diagnostic groups of diseases, would be worth examining in detail to see whether the effects of stress can be demonstrated because they are labelled psychosomatic. Norman (1958) examined the reasons for the differences in the experience of drivers, conductors, and workshop staff and some of what follows is a re-statement of his reasoning.

Functional Nervous Disorders

This broad diagnostic group consists of psychoses and psychoneuroses (codes 300–318 of the International Classification). Numerically, the psychoneuroses far outweighed the psychoses and any trends in this group were, therefore, due almost entirely to the former.

Fig. 2 shows by five-year age-groups the average number of spells of sickness-absence per man per year from these causes for the same groups of staff and for the same periods as in fig. 1. Motormen and guards had a consistently lower rate than any of the other groups of staff. Even with 16,000 man-years of experience there were only 147 spells of absence due to these causes among the workshop staff, so there was some fluctuation in the rates, but there was no tendency for the incidence to rise with age. There was very little tendency for the incidence to rise with age in the drivers and no tendency to rise with age among the conductors except for the clear rise in the 50–60 age-group. In fact, apart from the spectacular rise in the older conductors, there was little or no general difference in the rates for functional nervous disorders among drivers, conductors, and workshop staff; and yet the workshop staff were doing work which, from general observation, did not differ from that done by tens of thousands of light-engineer-

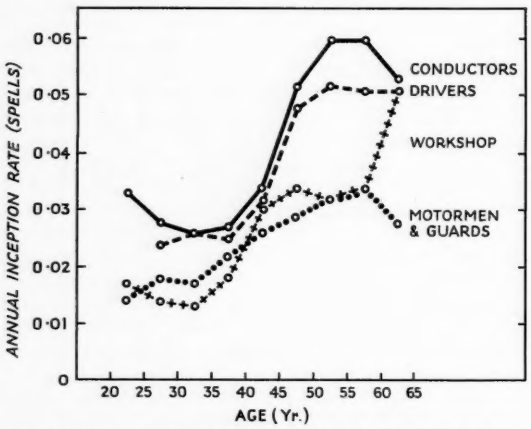

Fig. 3—Average annual frequency of sickness absence for diseases of stomach and duodenum 1949–52 (absence of 4 days or more).

ing workers in this country—work which could hardly be called "stressful".† It was surely among this group of disorders that some effect of stress would be found, unless stress produced physical illness in some men without previously, or at the same time, producing sickness-absence due to psychoneuroses in other men—an unlikely theory. The rise in the incidence of sickness-absence among the older conductors was unlikely to be due to stress alone, because it is difficult to imagine that stress would affect these age-groups alone and be completely ineffective at younger ages.

It is interesting that there was no evidence that shift-work had any effect on the incidence of functional nervous disorders. Drivers, conductors, and motormen and guards worked rotating weekly shifts, whereas the workshop staff worked normal factory hours, yet the motormen and guards had the lowest rates and the rates for drivers, workshop staff, and young and middle-aged conductors were virtually the same.

Diseases of Stomach and Duodenum

This broad diagnostic group consists of peptic ulceration, gastritis, duodenitis, disorders of function of the stomach, and symptoms referable to the upper gastro-intestinal tract (codes 540–545 and 784 of the International Classification). In general the frequency of sickness absence due to this group of disorders was three to four times that of functional nervous disorders. This is a group of disorders where emotional factors, and stress in particular, are often cited as a contributory ætiological factor. Norman (1958) pointed out that, because Avery Jones and Doll (1951) found peptic ulceration no more common in bus drivers and conductors than in industrial workers generally, then any difference in the rates of sickness absence for the whole broad diagnostic group between bus staff and workshop staff must be due to differences in the rates for other conditions than peptic ulceration—such as functional dyspepsias. Fig. 3 shows the results for this group of disorders.

Within the limits of variation due to smaller numbers, there was virtually no difference in the incidence of these disorders between motormen and guards and workshop staff (fig. 3). There was a steady rise in the rates with age. Except at the old ages, there was little difference in the experience between drivers and conductors. The difference between all four groups in the 35–45 age-groups was small compared with the differences at the younger and older ages.

Norman (1958) pointed out that at one time the idea that bus drivers and conductors suffered unduly from gastric disorders was firmly believed, even among doctors. It is evident that this belief, if it still existed, did not affect medical certification, otherwise the difference between the bus staff and the others would have been as apparent at all ages, whereas it nearly disappeared in the middle ages.

Equally, if the difference between bus drivers and conductors, on the one hand, and workshop staff and motormen and guards, on the other, was due to stress, then why did the difference nearly disappear in the middle ages to reappear at the older ages? This argument, taken with similar arguments put forward about functional nervous disorders, makes it unlikely that stress alone explained these differences.

It seems more likely that the differences at the younger ages were due to shift work.

Most of the conductors in the youngest ages were new to bus work, and probably to shift work. Some of the younger drivers were promoted from conductors and were, therefore, becoming accustomed to shift work. The rest of the drivers, who had substantial driving experience before joining London Transport, were also to some extent accustomed to bus work and shift work. The motormen and guards, because they were all promoted from station staff, had already had some experience of shift work, and would, therefore, be expected to have had a better experience than the drivers. If this effect of shift work was real, it is not surprising that in the middle years the experience of all four groups was little different because, by these ages, many of the men in all four groups already had long experience of transport work and had become accustomed to the work, including shift work. Those who could not adapt to shift work were likely to have left the service.

Shift work is unlikely to account alone for the differences found at the older ages, otherwise the incidence among the motormen and guards would also have been expected to be high. Possibly stress was the explanation of the differences at the older ages, with a conductor's job more stressful at older ages than a driver's. When the rise in the incidence of functional nervous disorders in the older conductors is remembered, it seems possible that stress had some effect in the 45–65 age-groups. But stress alone is unlikely to explain the higher rates for drivers and conductors, compared with workshop staff and motormen and guards, because there was a rise in the drivers' rates at older ages for gastric disorders without a corresponding rise in the rates for functional nervous disorders. For stress alone to be the explanation for these findings would mean postulating a form of stress which affected the digestive tracts of drivers and conductors at older ages and produced psychoneurosis in conductors only at the older ages and not at all in drivers.

There seems to be another possible explanation for these results—that is, that at later ages another—physical—factor was introduced. This could be that both drivers and conductors were getting more physically tired at their work than motormen and guards and workshop staff, and that conductors became more tired than drivers.

The postulates which appear to fit the observed sickness absence rates for all four groups of staff for both groups of diseases are:

Stress as defined is not an important factor in the production of either group of diseases. Shift work alone does not

† If the actual number of spells of sickness-absence attributed to functional nervous disorders, experienced by the conductors and the workshop staff, is expressed as a percentage of what they would have had if they had had the same rates of incidence, age-for-age from 25 to 65, as the drivers, the conductors had 103% and the workshop staff 108% of what they would have been expected to have had at the drivers' rates.

explain all the differences found; but shift work may explain the differences in the rates for gastric disorders at the younger ages in drivers and conductors. Fatigue may explain the differences in the rates for gastric disorders of both drivers and conductors compared with the other two groups at older ages, and possibly fatigue and stress together explain the differences between drivers and conductors at the older ages in both gastric disorders and functional nervous disorders.

These are clumsy and unsatisfactory postulates, especially as they do not take into account the findings for coronary heart-disease. When it is remembered that conductors had less coronary heart-disease in less severe forms than drivers, and yet had more sickness-absence from functional nervous disorders and diseases of the stomach and duodenum, the case for stress as a common factor in producing diseases of these three types becomes very weak. It does not, of course, exclude different types of stress producing different types of disease, nor does it exclude a common factor of stress acting differently in men of different constitutions, such as might have selected themselves into the two occupations.

Conclusions

Using the data for coronary heart-disease in bus workers and the population generally, and the occupational sickness-absence statistics for all causes, functional nervous disorders, and diseases of the stomach and duodenum for four groups of transport workers, the epidemiological evidence that stress is a factor in disease is, at best, tenuous. There are enough diverse external stimuli due to occupation in the working groups studied and enough different types of data of morbidity and mortality analysed, for stress to be expected to show up strongly somewhere in the evidence, if it is a factor in the production of disease in these men. In fact, in these data, if stress exists at all as a factor, it is a minor one. It is clinical experience that some external psychological stimuli disturb the organism to the point of mental or physical illness. It is a clinical impression that occupational stress can do the same. There would seem to be two reasons why the epidemiological evidence does not support the clinical impressions. The first is that, as clinicians, we generally see only those patients who have broken down under stress—whether occupational, social, or personal. Until stress can be measured directly, and not by inference from its effects, it will not be known whether the clinical impressions are correct or a fashion—a fashion to be dispelled just as the fashion of the busman's peptic ulcer was dispelled by the work of Avery Jones and Doll (1951).

The second, and more likely, reason for the paucity of epidemiological evidence of stress as a factor in disease is the effect of selection on the composition of occupational groups. A man who is going to find an occupation stressful is less likely to choose to enter that occupation than a man who will not. If, having entered the occupation, a man finds it stressful then he is more likely to leave it than a man who does not. In the end, therefore, each occupational group would tend to consist of those men who can do the job, or jobs, without showing strain. There will be men who, because of ambition or obsession, will not give in, and will stick to the job in spite of unfavourable reactions to it; but the epidemiological evidence suggests that there are not many. This effect of selection has further important implications. In occupations which need successive promotions, the additional effect of the employer's selection has to be taken into account. The employer generally promotes only the able man and is unlikely to promote the man who reacts unfavourably to pressure of work. The men at the top are, therefore, doubly selected. Only those who know that they can, and have shown that they can, withstand stress reach the heights. If this is true—and our politicians, top Civil Servants, and captains of industry have yet to be shown to have an unfavourable sickness record—then perhaps we should discourage the top executive from talking about the stress of his job and encourage him to welcome the pressure of his work as an index of his proven ability and toughness.

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UROLOGY AS A SPECIALTY

THE following memorandum has been drawn up by the council of the British Association of Urological Surgeons:

It is considered that whereas urology has progressed to a position of major significance among the surgical specialties this fact has failed to evoke a logical response in many areas. It is nowadays necessary in the interests of accurate diagnosis, reduction of operative mortality and morbidity, and the promotion of effective clinical care that such work should be segregated under surgeons specially trained or experienced in the conduct of the specialty. Some reorganisation of the surgical services in such centres where urological surgery is on a precarious footing is, therefore, urgently required.

While it may neither be possible, nor even desirable, for all cases of surgical disease of the genitourinary tract to be directly under the control of a urological surgeon, an immediate aim should be to create a sufficient number of urological departments (with appropriate geographical dispersal) to ensure that any patient in need of skilled urological care can be accepted without delay. There are many well-trained urologists whose special experience is not being fully exploited at the present time and who can be deployed into such departments with great advantage to the medical service. Failure to do so is in fact deterring many promising young men from seeking training in urological departments.

Reasons advanced for seeking recognition are that specialised techniques are often necessary for the effective treatment of urological conditions and these can neither be readily nor quickly acquired by the general surgeon dealing with only a small number of cases. Similarly, the standard of investigation and treatment of common urological disorders is in general felt to be more efficient when such cases are segregated in a urological department. Whereas urology has been recognised as a specialty in many parts of the world and by the Department of Health for Scotland (where a small number of special departments have already contributed greatly to the efficiency of the service) no comparable arrangements exist elsewhere in Great Britain. As a result, attempts to promote a urological service in the remainder of the country have proceeded in a haphazard manner, it being left largely to individual consultants to develop

local units often in the face of difficulties directly related to the absence of official support. It is felt that the only way to regularise the position and improve the general standard of urological care lies in the wider recognition of urology as a specialty with the formal establishment of approved departments of adequate size under the care of fully trained consultants who should be on an equal administrative footing with their general surgical colleagues. Such an arrangement would go far towards improving the prospects of senior registrars who have supplemented their general surgical experience by special training in urology and who wish to continue in the specialty on acquiring a consultant appointment. At the same time the official recognition of urological departments would tend to attract more promising young men to the specialty and thus relieve many of the existing difficulties in relation to junior staffing.

With regard to the establishment of a urological service throughout the country, it is suggested that this should be carried out in stages. Every teaching hospital should have a urological department staffed by a senior and junior consultant (each specially trained or experienced in genitourinary surgery) so as to provide continuity of care and ensure the training of successors. All large regional hospitals (supporting 150 or more general surgical beds) should likewise establish departments on similar lines, and the same should apply to selected smaller provincial hospitals where a large catchment area and lack of facilities warrant such a service.

It is particularly stressed that such departments should be of sufficient size and importance to enable them to take their appropriate place in the surgical activities of the hospitals concerned. Estimates of the range of cases treated in large hospitals indicate that genitourinary conditions account for between 20% and 25% of the surgical work, and it is suggested that this proportion should be envisaged in planning new units. Urological consultants should remain on an equal footing with their general surgical colleagues and there should be outpatient clinics devoted to urological cases. Supplementary staffing would be required on at least an equal scale to that existing in general surgical units and senior urological registrars should be appointed for training in all principal hospital units. The latter should be men trained in general surgery by having served first as registrars and thereafter for a minimum period of two years as senior registrars. On the assumption that men aiming to be urological consultants should spend at least four years as senior urological registrars, an increase in salary after their second year in this category (their fourth as senior registrars) should be granted.

The council recommends :

1. That formal recognition of urology as a specialty should be sought from : (i) the Ministry of Health and its regional Boards; (ii) the universities and their medical schools ; (iii) the Royal Colleges of Surgeons and the Royal Faculty of Physicians and Surgeons of Glasgow; (iv) the profession at large.

2. That officially recognised urological departments should be established in all teaching hospitals, all large general hospitals, and certain selected provincial hospitals on the lines suggested in the above report. It is recommended that this plan should be adopted in stages with a transitional period to allow of internal administrative readjustments.

Dialogues of Today

BIRTHS, MARRIAGES, AND DEATHS

SOCRATES: How many people do you think there should be in the world, Enthusiasticus?

ENTHUSIASTICUS: As many, I suppose, as the world's resources can support, and certainly no more.

SOCRATES: And by " support " do you mean merely provide them with enough to eat?

ENTHUSIASTICUS: No, in my view living means enjoying the fullest possible life of thought and feeling rather than mere bodily subsistence.

SOCRATES: You speak as if there were some conflict between a full life and mere living.

ENTHUSIASTICUS: Indeed there is, for if the population of a country is so large that it has a struggle to keep alive it cannot accumulate the reserves it needs to devote to education and culture and all the enrichment of life that springs from them.

SOCRATES: And how many countries can afford to do that?

ENTHUSIASTICUS: Very few, for in most countries of the world the majority of the people are chronically undernourished and even from time to time suffer from actual famine. In the past epidemic and endemic diseases kept their populations down, and even then their food-supplies were inadequate, but now preventive medicine saves so many lives that populations are in danger of outgrowing their production of food and other necessities.

SOCRATES: Has mankind, then, to choose between pestilence and starvation?

ENTHUSIASTICUS: There is a third choice possible. Man can learn to control his numbers by regulating the birth-rate.

ERYTHRO: To my mind that is a counsel of despair, Socrates. The present plight of the world is the result of the social order and the exploitation of man by man inherent in the capitalist system. All we need is a rational social order and the world could produce enough to provide a full life for a far larger population that it has now.

ENTHUSIASTICUS: Whether or not Erythro is right about the social order no-one supposes that world production can be reorganised on that scale for many years, and meanwhile rapid population growth in itself makes it more difficult to bring it about.

SOCRATES: What do you say, Theologus?

THEOLOGUS: I believe it to be a divine injunction that the human race should be fruitful and multiply, so I have what you would perhaps call a prejudice in favour of population growth. Every additional immortal soul must be an enrichment of the universe!

ENTHUSIASTICUS: Even so, they need not all come at once, surely!

THEOLOGUS: I agree. And therefore I accept the principle of controlling the birth-rate, provided the method employed is not sinful.

SOCRATES: What do you mean by sinful?

THEOLOGUS: Any act contrary to divine or natural law is sinful.

SOCRATES: I gather that authorities differ about the divine law in this matter, so tell us what the natural law is.

THEOLOGUS: Even that is part of the divine order. Sexual intercourse has two purposes, to procreate children and enrich the emotional bond between husband and wife. It is contrary to natural law that these two objects should be voluntarily separated. Hence to seek sexual satisfaction without being willing that the act should have its natural end is contrary to natural law, and methods used for this purpose are unnatural and sinful.

SOCRATES: Do you hold, then, that intercourse is sinful if it occurs when the wife is already pregnant, or sterile as a result of an operation, or when she has passed childbearing age?

THEOLOGUS: Certainly not, for in those instances there is no intention to avoid the biological consequences. The fact that no child can result springs from other causes.

SOCRATES: But does not your authority agree that those who for good reasons wish to avoid children may rightly limit their intercourse to those times when there is a physiological reason for thinking that pregnancy will not result?

THEOLOGUS: That is so. In the ordinary course of nature intercourse will occur at such times, so there can be nothing contrary to natural law in that.

SOCRATES: I feel rather confused, Theologus, and I hope you can clarify things for me. You said that it is wrong wilfully to separate the personal and the procreative objects of intercourse, and that the methods used for this purpose are unnatural. Are you not now saying that it may be right to separate these two objects of intercourse provided the method employed is natural? Is it the intention which is sinful or only the method employed?

ENTHUSIASTICUS: It seems to me, Socrates, that Theologus regards anatomical methods as unnatural, and physiological ones as natural, so I hope that when the physiologists find a way of naturally regulating fertility it will meet with his approval. But I believe he is the victim of a verbal muddle. What does natural mean? Isn't the human mind natural, and if it discovers through increasing scientific knowledge better ways of controlling man's own nature, why is that more unnatural than shaving or wearing clothes or having operations or taking drugs made in a laboratory?

ANALYTICUS: I would go further than that, Socrates, and ask Theologus why what he calls unnatural should be sinful. Is it perhaps significant that we are discussing a sexual question? I suspect that his reasoning is influenced by disguised emotion, and that an unconscious and hence irrational guilt feeling is at the bottom of his sense of sin.

THEOLOGUS: I should be sorry for a society which succeeded in eliminating the sense of guilt. For me at least the divine law is absolute.

ENTHUSIASTICUS: Not for the first time, Socrates, Erythro and Theologus seem to me to have a good deal in common. They are both religious devotees of an absolute principle. Theologus can decide whether a course of action is right or wrong only by making a deduction from his first principles in exactly the same way as a judge decides a point of law. And, like a judge, Theologus has his statute law and his case law to guide him. Sometimes the decision is easy; sometimes it is very difficult, especially when the law has to be applied to circumstances which were beyond human contemplation when it was made. I believe these questions have to be decided quite differently. Man has certain values, and his acts should be judged by whether, as far as reason can guide him, they promote or hinder those values. To neglect to take measures of population control at present is to promote illiteracy, hunger, abortion, disease, and death. We *must* limit the birth-rate if civilisation is not to perish. What methods it is right to use for this should be decided, not by an abstract definition of what is natural, but by the simple test of whether, so far as we can judge in practice, they promote the health and happiness of those who use them.

Medicine and the Law

Negligence in Failure to Detect Fracture

A MAN, employed as a laundry manager, fell from the roof of the laundry to a concrete floor some 12 ft. below. He was taken to the outpatient department of a hospital, where he was examined by a doctor who failed to detect any fracture.

The doctor dressed certain minor wounds, marked the hospital card "no clinical fracture" and allowed the patient to go home, telling him to return for further treatment. Three days later he returned to the hospital and saw a second doctor, who was informed that the dressing on one knee required changing. This doctor looked at the minor abrasion on the knee and changed the dressing, after informing himself about the case from the hospital card. After a further 10 days, during which the patient may have gone to the hospital several times, he was seen at the hospital by a third doctor, to whom he complained bitterly of severe pain in the knee. This doctor, after consulting the hospital card, told him that he had sinovitis in the knee and must expect it to be painful, replaced the bandage, and prescribed rest. After a further two days the patient saw a surgeon privately, and it was discovered that he had a patella broken into 11 pieces, a broken nose, and a hair-line fracture of the wrist. The patient then decided to obtain treatment privately, and entered another hospital, where an operation was performed on the knee. Because the tissues of the knee had become friable, the operation was difficult, the stitches placed in the knee tore out and a further operation became necessary. Convalescence was protracted, and he was left with instability of the leg.

The patient sued the laundry for, inter alia, negligence in permitting the laundry premises to be unsafe, and the hospital management committee and the first doctor who inspected his knee in respect of their failure to diagnose his injuries correctly and give him proper treatment. All the defendants denied liability.

Mr. Justice SALMON, having given judgment in favour of the laundry, said that it would have been astonishing if the patient, weighing 14 stone, had not done himself considerable harm in falling. There were many cases where a doctor might make a wholly wrong diagnosis without being negligent. No doctor guaranteed that he would always be right, but if the patella were broken into 11 pieces, it would have been impossible to miss it in the circumstances unless there were negligence, or, indeed, gross negligence. The case for the hospital and the doctor was that such a thing was so incredible, showed such a high degree of negligence, that his Lordship should conclude that the knee must have been fractured later. However, he had come to the conclusion that the knee had been broken and that the doctor had missed it, allowing himself to be put off by the patient's anxiety to go home. Had the doctor been more careful he would not have allowed himself to be put off by what was said by a man who was clearly suffering from concussion. The doctor had also missed the broken nose and wrist. The latter injury was very difficult to diagnose, and although most doctors would have detected it, or been suspicious and taken an X ray, his Lordship did not consider that the doctor was negligent in this respect.

His Lordship acquitted of negligence a hospital orderly, who had given the patient penicillin injections, and the second doctor. He had reluctantly to convict the third doctor of negligence, for after the patient's bitter complaints of severe pain she should have examined the knee, despite the entry on the hospital card, and would inevitably have found the fracture.

Upon the question of damages, his Lordship said that only a part of the patient's present disability, pain, and discomfort was due to the negligent failure to diagnose and treat his injuries. The operation on the knee should have been performed within two or three days of the accident. Its postponement for over a month had necessitated two operations in place of one, and had exposed the patient to excruciating pain which was wholly unnecessary. After his experiences it was eminently reasonable for the patient to obtain private medical treatment, though it was not reasonable for him in all the circumstances to employ a specialist nurse and the defendants would not have to pay for this. The patient had suffered no loss of earning power for the future, but had been out of action for six months longer than was necessary. He should receive £650 for additional suffering and residuary disability caused by the negligence at the hospital, and £778 for his medical expenses and loss of earnings in the past.

NEWTON *v.* NEWTON'S MODEL LAUNDRY LTD. AND OTHERS. *Queen's Bench Division:* Salmon, J. Nov. 2, 1959. Martin Jukes, Q.C., and Harold Marnham (Parlett, Kent & Co.); J. D. May (Davies, Arnold & Cooper); Michael Lee (Eric G. Marshall); J. T. Molony, Q.C., and Owen Stable (Hempsons).

GROVE HULL
Barrister-at-Law.

In England Now

A Running Commentary by Peripatetic Correspondents

WE have always felt very close to our dustmen. Week after week we have watched them work their weary way to the front door, collect our varied rubbish, and depart. We have become used to interrupting their little clandestine meetings in the secluded mews outside our garage where they explore their spoil and pick out any small saleable junk. Occasionally, after some national holiday, their routine has been disturbed and for several days a deposit has accumulated round our front door, almost preventing access, until their beneficent cycle is restored to normal. We have taken pride in their new machinery—the replacement of a sort of open cart by a semi-cylindrical lorry with slots down each side, which has in turn given way to a long device which enchants the kids by rising to 90° in the air to tip the accumulated refuse to one end.

It was with interest, therefore, that we greeted, two weeks ago, the advent of an efficiency expert who stood outside the gate with a small book and watch, noting what was brought out of each gate. "He's the censor," explained one of our dustmen to my fascinated wife. "He sees 'ow many bins people 've got." It appeared that the statutory limit was one bin per family. Asked what would happen if we bought another bin surreptitiously and left it outside, he replied: "Well we'd empty it of course—fing is, there's a lady up the road wot 'as seven." Conjecturing what sort of life this lumber-bound lady led, we welcomed this invasion by time-and-motion; not that we expected much from it. After all a dustman is still a dustman, call him never so often a refuse operative. The grand result of this careful study was revealed today. We received a Notice to Householder which ran "House Refuse Collection Service (Re-organisation)—In future your normal day for collection of refuse will be MONDAY. Sgd., Borough Engineer and Surveyor." Oddly enough it's been Monday ever since we moved in, ten years ago. Nothing like progress is there?

* * *

There we were, at least a quorum (collective noun for dodos, elder statesmen, representatives of this and that, brash young things on the far side of fifty, and some industrious and unassuming secretarial bodies). Our common experience, if laid flat end to end, would reach from the later Middle Ages to just before the discovery of penicillin.

There was the agenda, which arose out of the last agenda and so on, back to the forgotten past when Creation willed its own existence: genealogically the First Cause was generally felt to be responsible.

The lists were entered, tea brought round, sparks flew, making beautiful condensation tracks in the misty dust-laden atmosphere. After two hours, when the chairman had to catch a train, all was resolved into minutes from which, doubtless, the next agenda would phœnix-like arise, ever young, ever the same.

Were the tea leaves perhaps destined for some useful purpose, I wondered, such as nourishing a rose?

* * *

This last week I have been cook, messenger boy, telephone operator, bandage-winder, launderer, and ward-maid to a patient home from hospital with a surgical wound, healing but still discharging. This patient is allergic to many things, including hospitals and spiders, but worst of all she is allergic to 'Elastoplast' and to ordinary strapping. Her skin comes up into huge weals, which break and leave a nasty painful raw surface. The wound was in an awkward place on the outer aspect of the thigh, about 6 in. below the hip-joint. How were we, the doctor, the district nurse, and the cook-ward-maid, to persuade the dressing to stay in place? One of the hospital nurses said that the patient would have to put up with her allergy and would not take "no" for an answer. So the poor lady lost skin. But we were in a weaker position. We shrivelled at the thought of a flayed ham. Besides, the patient stated in emphatic language what she'd be before she'd stand it and where we could go if we did it.

Impasse, till I remembered that when the patient damaged her fingers in the past she used to cover the wound with stamp-edging and with no sign of allergy. Of course the skin of the thigh isn't as tough as that of a finger, but spurred by necessity, we tried stamp-edging over one of the patches of allergic skin. It worked. Or, rather, it didn't work. The skin under and around the stamp-edging remained normal.

Now stamp-edging wouldn't be strong enough for the main dressing. Besides it is in short supply in most homes. I had used up all the stamp-edging of a pound's worth of penny-hapenny stamps in our minor experiment. Anyhow, I couldn't face the officials in our post-office with a demand for 10 yd. of stamp-edging. Suddenly a brainwave! We had in the house an enormous roll of that revolting gummed strip paper with which packers make it impossible for recipients to open a parcel. The gum tastes like death having a mixed flavour of decomposing fish, treacle, sealing-wax, liquorice, and disinfectant when you lick it. Would it hold the dressing in place? No allergy after 24 hours. And it can be removed by a damp sponge! None of your ether or surgical spirit. Great discovery! You can bandage a live patient with sticky paper, just as efficiently as you can seal a dead parcel. Why spend money for strapping when sticky paper will do the trick?

* * *

One of my colleagues was telling me yesterday with pride about the prowess of his three-year-old son, who had been left alone in the bath-room with a hammer for not more than 10 minutes. During this time he broke the lavatory pan, flooding the floor and the ceiling below, smashed the mirror, chipped the bath, knocked the top off the electric water-heater so that the entire hot-water container boiled dry, and then threw the hammer through the (closed) bath-room window and the roof of the conservatory underneath it. The bill came to £186. Is this a record for accident proneness?

* * *

It was our first visit to Florence and we were sure that we did not want a guide. But a local friend insisted we must secure Signor X; we would never regret it.

Reeling from the impact of our first sight of the facade of the Uffizi, we met him in the corner of the Piazza della Signoria beneath vast statuary depicting the rape of the Sabine women. "Classical cocktail party," he said, and took us into the gallery. There, confronted with the gold and scarlet of the Sienese altar pieces, he brought to life with rare rhetoric the glitter, noise, and spiritual climate of 14th-century Italy. Quick, perceptive, birdlike, not a day under 70, he unrolled the vast canvas of the history of the Renaissance in Europe with a distinctive and slightly non-European slant. Declining to stop for coffee, he rebuilt the Duomo for us stone by stone; with him we relived the horrors of the bubonic plague, the shock of the martyrdom of Savonarola.

He had escaped with his life from the October revolution; and for over forty years he has been opening wide the eyes of the unenlightened to the birthright he had so early lost.

* * *

OBJET TROUVÉ

Cars
Don't move me to *extase*
When salesmen talk to me
I feel *ennui*
In London *c'est plus vite*
To use one's feet
And when it's misty—
Sapristi!

But *tout de même*
To walk is rather tame;
A man who does not drive is thought a freak
C'est symbolique
And so I can't deny
That it's a rare *trouvaille*
This *objet d'art*
My car.

Letters to the Editor

CANCER IN ULCERATIVE COLITIS

SIR,—Mr. Slaney and Mr. Brooke (Oct. 31), like many other workers in the field of ulcerative colitis, stressed very rightly the risk of cancer and particularly its high incidence in those patients who have had the disease for ten years or more. They also point out the very poor prognosis in this group of patients, who are usually relatively young.

In the medical treatment of ulcerative colitis this risk is often ignored and the disease allowed to continue in subdued condition for many years. Eventually a considerable proportion of such cases are referred to the surgeon when cancerous change has already spread too far for practical excision.

It seems logical therefore to suggest that if after a full regime of medical treatment and of constant supervision lasting three years or so symptoms persist, or if X-rays and sigmoidoscopies show widespread persistence of the disease, operation should be recommended. Further medical treatment is most unlikely to effect a cure, and always present is the spectre of the development of cancer.

This, as I read it, is the line of action that Mr. Slaney and Mr. Brooke suggest and they have my whole support. Where I part company is over the best type of operation. I and my colleagues at The Gordon Hospital have no doubt that the rectal changes present in the condition are not irreversible except in those cases of many years' standing where chronic fibrosis and stricturing are present or where a high fistula has formed. Ulceration will heal and the inflammatory changes resolve provided the whole of the colon is removed and ileo-rectal anastomosis is completed. The exceptions to this are but a minute minority of all cases.

We can therefore offer to these patients with chronic disease not only the elimination of a very real chance of the development of cancer but also the opportunity of a return to 100% good health and the avoidance of an ileostomy, except over the immediate operative period. Mr. Slaney and Mr. Brooke advocate the removal of the rectum partly because they feel that if it is left cancer may develop there. This risk must indeed be slight. At The Gordon Hospital over 170 cases have been operated upon by total colectomy and ileo-rectal anastomosis. Only 1, a case of my own, has developed a cancer in the rectum, and I believe that this was present although unrecognised before operation was undertaken. He was a young man of 19 in whom the disease had begun at 2 years old and in such a longstanding case as this I would now agree that removal of the whole of the large intestine including the rectum may probably be the safer operation. One can hope, however, that such longstanding cases will become increasingly rare.

Finally, in my own personal series there has been an incidence of cancer, inoperable in most cases, of 7%. Only 1 has survived four years. The operative mortality for total colectomy and ileo-rectal anastomosis, including all fulminating and acute cases, has been 5%. Of the chronic cases, in which category those under consideration would fall, the mortality has been 1 amongst 68 patients. There is no doubt, therefore, that the risk of development of cancer is many times greater than that of operation. If chronic though not completely incapacitating disease has been present for more than three years the conclusion to me seems inevitable that total colectomy and ileo-rectal anastomosis is the only operation that will find acceptance by both physician and patient and is in my opinion the sole method of treatment that should be urged.

London, W.1. STANLEY AYLETT.

DOMICILIARY REHABILITATION OF THE RESPIRATORY CRIPPLE

SIR,—Mr. Capener (Oct. 24) has been justifiably impressed with the Danish Government's attempts to rehabilitate their respiratory poliomyelitis cripples, and suggests that more could be done for these people in Great Britain. This is certainly true. Money is what is needed most, but a start can be made with less bureaucracy, as these two examples show:

(1) An attempt to get a rocking bed for a patient to use at home is still before committees after nine months. The Ministry of Health say the supply of such equipment is the concern of the management committee, but management committees are not keen on ordering equipment for patients to take home. As the Ministry supply wheel-chairs for the patient who cannot walk, surely a respirator for a patient who cannot breathe should come in the same category.

(2) Many of my severely paralysed patients go home for weekends or for longer periods. For geographical reasons, three ambulance services are used. Two have been most helpful, but the third has just refused to transport patients more often than some arbitrary maximum laid down in the office, an edict which no doubt we will be able to get rescinded, but only after much time has been wasted.

There can be no general solution suitable for all types of respiratory patients. For some, the ideal is undoubtedly complete adaptation of the home to accommodate the patient, but I am not convinced that this is the best solution for all, even if the expense and nursing difficulties did not make it so hard to attain. A compromise with alternating periods at home—for as long as the relatives can conveniently manage—and in hospital works well in practice. There is no doubt that the periods of respite are much appreciated by relatives, however devoted they may be. I would suggest that a central authority, probably the Ministry of Health, should have funds set aside for the supply of respirators needed for patients' use in their own homes, and for carrying out modifications to houses, whether council or private (such as widening doors, altering lavatories, &c.), that may be required for such patients.

London. G. DONALD W. MCKENDRICK.

ÆTIOLOGY OF PICA

SIR,—It may be interesting to recall that views somewhat similar to those recently expressed in your columns on the origin and cure of this symptom were held in England in the early eighteenth century—a time when it was probably much more common here than it is now. In his *New System of the Spleen, Vapours and Hypochondriack Melancholy* (1729), Nicholas Robinson takes this symptom as an example of the ways in which bodily disturbances can affect mental activity. He says (p. 69):

"I shall beg leave just to touch upon the causes of those irregular turns of thought, and false appetites that often affect young girls under the green sickness, and why they covet things disagreeable to their natures, and which they themselves would loath under a state of health.

Who would think it possible, did not daily experience convince us of it, that a thin, pale, meagre girl should covert toasted coals before wholesome food, or prefer the cranching of dirty lime and tobacco pipes before the most delicious viands, or the harsh noise that arises from treading cinders under foot, before the most melodious music?

and yet in fact I am able to produce numberless instances in confirmation of these cases. And that these strange and unnatural desires arise only from a perverted motion of the solids and fluids, is clear; for if, by proper applications, you recover these bodily organs to their regular standards again, these unnatural desires and strange unusual fancies will vanish of their accord."

The Bethlem Royal Hospital, Beckenham, Kent. E. H. HARE.

IPRONIAZID AND IMIPRAMINE IN CHRONIC DEPRESSION

SIR,—We have successfully treated a case of chronic depression with a combination of iproniazid (' Marsilid ') and imipramine (' Tofranil ') in much smaller doses than generally used. This seems to us worthy of note in view of the fact that iproniazid is rather toxic.

A 57-year-old widow had suffered from a severe chronic depression since 1957, for which no treatment, including E.C.T., had hitherto been of avail. In September, 1958, she was given 200 mg. of imipramine daily for about two weeks, but no definite improvement resulted. In March, 1959, she was given 150 mg. of iproniazid daily for eight weeks. She grew better, but when she stopped taking the drug after she left hospital her depression came back. She was readmitted to the hospital in the autumn of 1959, and was then given 75 mg. of iproniazid a day for two weeks, and after that 25 mg. of imipramine a day as well as the iproniazid. Two days after she began having both drugs, her depression vanished, her pulse rose from an average of 70 to 80, and at the same time she began to feel a little dizzy, and had short attacks of sweating and a feeling of dryness in her mouth. Later the dose of iproniazid was reduced to 50 mg. daily without the depression returning.

Though it is clearly difficult to judge the result in this case, we thought it worth reporting in view of the interesting possibilities in this combined form of treatment. It has been suggested that imipramine might be able to sensitise central adrenergic mechanisms to the action of catecholamines.[1] Further investigations are in progress.

Lillhagen Mental Hospital, Gothenburg, Sweden. GAYLER WHITE
BJÖRN-ERIK ROOS.

CLASSICAL HÆMOPHILIA OR VON WILLEBRAND'S DISEASE?

SIR,—I should like to support Dr. Merskey (Nov. 7) in his contention that the disease suffered by members of his famous family of bleeders [2] is hæmophilia rather than von Willebrand's disease (vascular hæmophilia). I have examined two affected males in this family and observed the response of these patients to trauma (dental extraction and removal of nasal polypi). I have also carried out laboratory tests on their blood before and after therapy. The level of antihæmophilic globulin (A.H.G.) before treatment in these patients has always been 0%. Their hæmorrhagic episodes have been of the hæmophilic type and raising the blood-A.H.G. level has controlled bleeding.

It is true that various members of this family have either a long bleeding-time or a positive tourniquet test, but so also do members of other hæmophilic families.[3] At the present time there is insufficient evidence for the strict categorisation of such difficult families, and their study may ultimately clarify the relationship (if any) between von Willebrand's disease and hæmophilia. At present it is certainly wise to regard each patient from the clinical and laboratory point of view to determine whether or not the defect is on the whole of the capillary or hæmophilic type. It is not possible to make a rule that any patient with both a long bleeding-time and a low A.H.G. level shall be classified as von Willebrand's disease. This point is not purely academic because a diagnosis of von Willebrand's disease suggests a relatively good prognosis for surgical treatment, whereas in hæmophilia operations must be accompanied by adequate antihæmophilic treatment. From this point of view members of Dr. Merskey's family certainly have hæmophilia.

The Churchill Hospital, Oxford. ROSEMARY BIGGS.

CANCER: TO TELL OR NOT TO TELL?

SIR,—When the prognosis is hopeless there will be few of the patients' relatives who object to the calling in of a solicitor to settle the family affairs. Is it fair then to the patient to let him meet his God without giving him an equal opportunity of settling his spiritual difficulties as far as a minister of religion can do so? Patients who have had this privilege often show by their calmness and reconciliation that their distress was not of physical origin.

Wolverhampton. PATRICK E. CARROLL.

PREVENTION OF STILLBIRTH IN Rh HÆMOLYTIC DISEASE

SIR,—After the article by Dr. Tovey and Dr. Valaes (Oct. 10) I think the following case deserves mention. It is an instructive example of the fact that, despite a very bad obstetric history of rhesus incompatibility (only 1 infant in 5 pregnancies survived the neonatal period), it is still possible, with careful antenatal supervision and induction of labour suitably early, to obtain a living child.

A housewife, now aged 28, is group-O, genotype cde/cde. Her husband is group-A, genotype CDe/cDE. In 1951 she became pregnant for the first time, and gave birth to a live female. The infant was Rh-positive and did not develop jaundice. No maternal Rh antibodies were detected antenatally.

In 1953 her second pregnancy was normal up to 30 weeks, when a macerated fœtus was delivered. No test for Rh antibodies was carried out as she had not attended for antenatal care.

In 1954 her third pregnancy progressed normally till term, when a live female was born. At 18 weeks, weak anti-Rh agglutinins in albumin only were detected, but by term these had risen to 1:256, (anti-D being 1:2048 with a weak anti-C), with a strongly positive indirect Coombs' test. The infant was group-O CDe/cde with a cord hæmoglobin of 72%, and died during the exchange transfusion. The interesting point about this infant was that at first it was thought to be Rh-negative, presumably because of severe blocking by the incomplete antibody.

In 1955, and again in 1956, her fourth and fifth pregnancies miscarried at 27 and 28 weeks respectively, a macerated fœtus being passed on each occasion. The maternal antibody titre was 1:128 in albumin during both pregnancies.

In 1958 she became pregnant for the sixth time. At 22 weeks maternal anti-Rh agglutinins were present at 1:2 in saline and 1:256 in albumin. At 30 weeks they were absent in saline, but had risen to 1:512 in albumin. Accordingly at 35 weeks labour was induced by rupture of the hindwaters, when the typical golden liquor was seen.

A live male of 5 lb. was born, and apart from slight jaundice was quite healthy. The cord hæmoglobin was 57%, and serum-bilirubin 8 mg. per 100 ml. with a strongly positive direct Coombs' test. After two exchange transfusions on the first 2 days of life, and a small " top-up " transfusion at 13 days, the infant progressed very well.

Some obstetricians have, certainly in the past, advocated sterilisation with or without termination of pregnancy in

1. Sigg, E. B. *Canad. psychiat. Ass. J.* 1959, **4**, suppl. p. 75.
2. Merskey, C. *Quart. J. Med.* 1951, **20**, 299.
3. Biggs, R., Macfarlane, R. G. *Brit. J. Hæmat.* 1958, **4**, 1.

severely affected cases and, in fact, the question was raised after this patient's third pregnancy. While not being over-optimistic, I think this case illustrates that some ray of hope may legitimately be held out to such unfortunate women and that more drastic measures should not be undertaken on this account alone.

I wish to thank Mr. F. H. Finlaison for permission to publish this case-history.

Lewisham Hospital, London, S.E.13. C. D. G. EVANS-PROSSER
Late house-surgeon, Old Windsor Hospital.

TREATMENT OF GALACTOSÆMIA

SIR,—In galactosæmia it is important that treatment should start as soon after birth as possible. This entails the production of a suitable lactose-free milk. It is technically difficult to remove all the lactose from casein, and synthetic milks made from casein can contain enough lactose to cause symptoms in the more severe cases.[1] Moreover, attempts to remove lactose may result in the removal of the best part of the B vitamins. Soya milks have been suggested, but soya flour contains a tetrasaccharide, stachyose, which on hydrolysis yields two molecules of galactose.

E. F. Armstrong,[2] who described stachyose in 1919, stated that it was not attacked by normal intestinal enzymes, but Holzel and his colleagues consider it imprudent to use soya, and advocate a synthetic milk (Moll's pudding) made from eggs, fat, and cereal. This is difficult to prepare as a milk, and is not well taken by infants. The cereal preparation recommended by Holzel et al. has recently been modified by the manufacturers and now contains lactose. We have therefore investigated the use of a new soya milk produced by A. Wander Ltd., London, W.1, under the name of 'Wanderlac'. It is made from processed soya flour with sucrose, dextrose, and other carbohydrates, but entirely free from lactose or galactose. This soya milk, which contains all the B vitamins, as well as the A and D vitamins, in milk, has been well taken by all the infants who have been offered it, amounting now to over 20 in different parts of the country.

The processed soya flour used in the manufacture of 'Wanderlac' was hydrolysed with boiling HCl and the liberation of galactose confirmed by paper chromatography. When the soya flour was incubated at 37°C with N/10 HCl for 2 days no galactose was liberated. Soya flour was then incubated with N/10 HCl and pepsin for 24 hours, neutralised and incubated with trypsin for a further 24 hours. No galactose could be found in the digest. 'Wanderlac' itself, when subjected to the same treatment, was not found to contain any free galactose.

Three galactosæmic infants have been treated at Great Ormond Street with 'Wanderlac'. One was first given a synthetic casein milk with no improvement. On 'Wanderlac' good progress was made clinically and biochemically until weaning commenced. When seen later as a routine check the mother had not noticed anything amiss, but galactose was found in the urine and the galactose-1-phosphate content of the red cells was raised to 1 μg. per ml. (normal level 0 to 0·2 μg.). Inquiry revealed dietetic errors, such as the use of margarine containing milk and of tinned baby foods, biscuits, &c. which did not disclose on the label that milk or lactose had been added. When these errors had been corrected, the infant progressed well on 'Wanderlac' with milk-free supplements, the galactosuria and aminoaciduria ceased, and the following results for galactose-1-phosphate were obtained: 6 weeks after galactose-free diet had been restarted, 0·6 μg. per ml.; 10 months after, less than 0·1 μg. per ml.

A second infant diagnosed and treated initially with success by Dr. J. H. Moseley failed to progress, and symptoms returned on weaning. On admission good progress was made on 'Wanderlac' alone, galactosuria ceased and aminoaciduria diminished. Galactose-1-phosphate was found to be 0·2 μg. per ml., but later, on a mixed diet, was 0·4 μg. per ml.

A third infant has been treated with 'Wanderlac' with good clinical results. Galactosuria and aminoaciduria have ceased, but no estimations of galactose-1-phosphate have yet been made.

We wish to thank Dr. Bernard Schlesinger, Prof. A. A. Moncrieff, Dr. Philip Evans, and Dr. J. H. Moseley for permission to publish these observations.

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1. Holzel, A., Komrower, G. M., Schwarz, V. *Mod. Probl. Pædiat.* 1957, **3**, 359.
2. Armstrong, E. F. The Simple Carbohydrates and the Glucosides. London, 1919.

CONJUNCTIVAL MICROANEURYSMS IN DIABETES?

SIR,—In your leading article of Oct. 24, it is claimed that aneurysms similar to those present in the retina are to be found in the conjunctiva of diabetic subjects. Reference is here given to the investigation by Cook.[1] It should be noted, however, that the term "aneurysm" in Cook's work was not applied to capillary aneurysms analogous to those of the retina, but to fusiform, saccular, and irregular dilatations of unspecified small vessels. His illustrations actually showed that these changes were observed in the venules. It is well recognised that such *aneurysm-like* dilatations in the venules are manifestations of the ageing process even in healthy subjects.[2–4]

In reinvestigating the whole question whether capillary microaneurysms analogous to those in the retina occur in the conjunctival vessels of diabetics, Ditzel and Duckers [5] examined 70 diabetic and 70 healthy children. Not a single case of such a microaneurysm was found. In addition, in a study of 150 normotensive diabetic and 90 healthy adult subjects, no specific conjunctival vascular lesions analogous to those in the diabetic retinæ could be found.[6]

Sundby Hospital, Copenhagen. JØRN DITZEL.

RISKS ASSOCIATED WITH ELECTROPLEXY

SIR,—In his letter of Nov. 7, Dr. MacDougall seems to have overlooked the two important points I raised—namely, the case for giving patients an intravenous barbiturate, with a relaxant, and the fact that the technique he refers to cannot be held to eliminate the risk of fractures or fracture-dislocations. I discussed the question of technique and method, not the results. At no time have I stated any adverse views on the *results* obtained in any group of patients, whether schizophrenics or manic-depressives, using the method to which he refers. I merely criticise a technique (and I still hold this view) which is unpleasant for the patient, and certainly not without the risk of fractures. In the light of our present-day knowledge we have no right to deny to patients with psychiatric illness the benefits of a smooth and pleasantly induced anæsthesia, and the protection afforded by modern short-acting relaxants.

1. Cook, C. *Int. Congr. Ophthal.* 1954, **3**, 1878.
2. Vogt, A. Lehrbuch und Atlas der Spaltlampemikroskopie des lebenden Auges; p. 142. Stuttgart, 1941.
3. Ditzel, J. *Circulation*, 1956, **14**, 386.
4. Knisely, W. *J. Geront.* 1957, **12**, 429.
5. Ditzel, J., Duckers, J. *Acta pæd. Uppsala*, 1957, **46**, 535.
6. Ditzel, J., Sagild, U. *New Engl. J. Med.* 1954, **250**, 587.

There is also a considerable body of opinion against giving patients E.C.T. every day (whether "modified" by relaxants, or "unmodified"), as is recommended by those who prefer to use the "intensive" method. E.C.T. is still E.C.T., no matter what name it is given or which type of apparatus is used. Quite apart from the debatable question of brain damage, about which we know little, do psychiatrists who use this method *honestly* claim they are making day-to-day clinical assessments of their patients, as we should do, regulating the frequency of E.C.T. according to the patient's individual requirements? I, for one, cannot believe it.

Carlton Hayes Hospital, Narborough, Leicester. MARTIN RAHILL.

THE GHANA MEDICAL SERVICE

SIR,—Please allow me to direct attention to the advertisement in this issue for doctors for work in Ghana.

I have just returned from Ghana, and I am greatly impressed by the enormous advances in every field of activity since my visit at the time of their independence in March, 1957, only $2^1/_2$ years ago. Magnificent modern architect-designed buildings are going up all over the country. The Ambassador Hotel built for the independence celebrations is on a level with the Park Lane hotels here, and is considerably cheaper.

The University is more than three-quarters built and is beautiful. Dinner in one of the halls combines the dignity of an Oxford or Cambridge college with the gaiety and colour of modern tropical buildings. Plans are advanced for a University College Hospital.

The climate is good, and a tourist trade is developing. No longer can the country be called "the white man's grave", neither is it any longer "the white man's burden".

I can confidently recommend doctors in the United Kingdom to take up posts in the rapidly expanding Medical Service in Ghana. English being the lingua franca, they will have an advantage over the doctors from non-English speaking countries. They will be able to assist Ghana in its efforts to become the leading democratic country in "Africa". The country is compact, with a population of only 5 million, a considerable sterling balance, and every prospect of becoming a stable prosperous country. We are not seeking "misfits".

C. BELFIELD CLARKE
Senior Medical Officer in London, Ghana Government.

New Barnet, Herts.

ENDOGENOUS HYPOGLYCÆMIA

SIR,—Our experience with spontaneous hypoglycæmia in children has been rather different from that of Dr. Kinsbourne (Oct. 17). We only wish that we found it as easy as his letter implies to decide whether a particular case should undergo surgery.

It now appears that the "syndrome of idiopathic hypoglycæmia of infants" as defined by McQuarrie [1] includes a variety of conditions of differing ætiology. As well as being classifiable into leucine sensitive and insensitive types depending upon the blood-sugar response to this aminoacid, some cases have been shown to have a high level of plasma insulin-like activity.[2,3] Also some cases are found to have hyperplasia of the islets of Langerhans,[4] while the pancreases of others are normal. It is hoped that newer methods of investigation will before long make fewer cases "idiopathic".

It has not been our experience, or the experience of some others,[3] that all cases of idiopathic hypoglycæmia respond well to treatment with corticotrophin (A.C.T.H.) or corticosteroids. Conversely corticotrophin may relieve the hypoglycæmia.[5] Thus response to corticotrophin is of no help in distinguishing the one type of case from the other.

We do not agree that surgery is a "last" and "often unavailing resort" in the idiopathic group. We have recently seen a child who had persistently low blood-sugars with hypoglycæmic symptoms despite large doses of corticosteroids over a period of two years, and in whom partial pancreatectomy has resulted in apparent cure. Several similar cases are recorded in the literature. We believe therefore that operation should be advised in those cases which do not respond to medical treatment within one to two years, and even if no tumour is found, subtotal pancreatectomy should be performed.

The Children's Hospital of Winnipeg, Manitoba. FISCHEL J. COODIN.

NEW WORDS REQUIRED

SIR,—In reply to your correspondent's request (Oct. 31) I suggest that "fluff" could be elevated into respectability. It already has most of the right meaning, and associations with immaturity or the wandering mind. I suppose it *could* be changed to "phluph" or "phlough" . . . and referred to as the φ-factor.

Workington, Cumberland. R. N. R. GRANT.

SIR,
Let colleagues blunder: when the blunder's mine
To dysreact is human, to forgive, divine.

Loughton. ALEX COMFORT.

BLOOD-GROUPS

SIR,—Dr. Wiener (Oct. 24) has criticised adversely a recent number of the *British Medical Bulletin* [6] dealing with blood-groups. I feel that I ought, as chairman of the editorial board, and in fairness to the editors and contributors, to point out that, on the subject of Rh groups, most workers take a contrary view to that of Dr. Wiener. It is impossible within the space of a letter to deal with the many complex considerations involved, and I would therefore refer readers to a previous detailed analysis.[7] The report [8] of the Committee on Medicolegal Problems of the American Medical Association, cited by Dr. Wiener, elicited a reply,[9] signed in alphabetical order by F. H. Allen and 32 other leading research workers engaged in blood-group investigation in America, in which they expressed their intention to continue using the C-D-E nomenclature until such time as a properly representative body should arrive at a definite nomenclature.

With regard to the relations between blood-groups and disease, the very paper [10] which Dr. Wiener criticises appears to me to refute his own arguments, apart from his remarkable suggestion that hospital records systematically confuse the blood-groups of patients and those of their donors. It may, however, be pointed out that the reason for the partial failure of earlier investigations was that the numbers examined were too small and it is only since much larger numbers have been examined that significant

1. McQuarrie, I. *Amer. J. Dis. Child.* 1954, **87**, 399.
2. Cochrane, W. A., Payne, W. W., Simpkiss, M. J., Woolf, L. I. *J. clin. Invest.* 1956, **35**, 411.
3. *J. Pediat.* 1959, **54**, 116.
4. Douglas, D. M. *Arch. Dis. Childh.* 1959, **34**, 171.
5. Roxburgh, R. C. *Lancet*, 1954, i, 1057.
6. *Brit. med. Bull.* 1959, **15**, no. 2.
7. Mourant, A. E. *Brit. med. J.* 1957, ii, 461.
8. Wiener, A. S. *J. Amer. med. Ass.* 1957, **164**, 2036.
9. Allen, F. H. et al. *Science*, 1958, **127**, 1255.
10. Roberts, J. A. F. *Brit. med. Bull.* 1959, **15**, 129.

results have been obtained with consistency. The subject by no means lacks a rationale—a very substantial beginning for its theoretical foundations was supplied many years ago by Sir Ronald Fisher and Dr. E. B. Ford—and it is now remarkable to read how in 1945 Ford [11] pleaded for just such investigations as Dr. Wiener deplores, and how accurately he predicted the course which discoveries from 1953 onwards would take.

The Lister Institute,
London, S.W.1. A. E. MOURANT.

LEUKÆMIA AND GEOGRAPHY

SIR,—The variations in leukæmia death-rates noted by Dr. Phillips (Oct. 24) may have a simpler explanation than he suggests.

In the period 1950–53, 26 of the 52 English and Welsh counties had leukæmia death-rates below the national average. In all but 5 of these 26, the death-rates increased during the period 1954–57. The 5 counties studied particularly by Dr. Phillips include 4 where the leukæmia death-rates in 1950–53 were well below the national average. No effect other than random fluctuations need be invoked to account for the increases during the succeeding 4-year period.

Since Dr. Phillips suggests that ^{90}Sr from radioactive fallout may be responsible for an increased incidence of leukæmia in mountainous areas of high rainfall on or near the Western coast, it may be worth mentioning that roughly comparable figures for Scotland, where terrain of this kind is common, have been calculated (by Miss Sheila Carter and Miss Aileen Falconer of this department) from the annual reports of the Registrar-General for Scotland. The following extract is relevant to Dr. Phillips's argument:

County	*Death-rates from leukæmia and aleukæmia, per 100,000 population per year*	
	1950–53	*1954–57*
Argyllshire	4·2	3·5
Ayrshire	2·8	4·4
Dumfriesshire	4·0	5·1
Dunbartonshire	4·0	3·0
Inverness-shire	3·5	6·0
Lanarkshire	3·0	4·0
Renfrewshire	4·0	4·4
Ross and Cromarty	5·0	8·4
Sutherland	11·4	5·7
Wigtownshire	2·5	4·1
Scotland	4·0	4·8

Here too there is no evidence of any but the random changes which are to be expected in a series of small samples.

Regional Physics Department,
Western Regional Hospital Board,
Glasgow. J. M. A. LENIHAN.

SIR,—The possibility that the incidence of leukæmia and other diseases is increased by radiostrontium fallout has, of course, been a source of concern for some time. Even if no more of this isotope is produced, there is still a considerable quantity of it in the upper layers of the atmosphere, sufficient to cause a steady accumulation in the earth's surface before finding its way into the sea. In turn this is bound to result in further accumulation of radiostrontium in animals and in man,[12 13] resulting in several hazards, of which leukæmia is only one. The analysis of deaths from leukæmia by Dr. Phillips (Oct. 24) lends further support to this fear. It is desirable, therefore, that some organised attempt should be made to counter this hazard.

One approach is to concentrate on research into the levels of radiostrontium in the bones of patients with leukæmia. But surely the problem is too pressing to be tackled on the small scale suggested by Dr. Phillips? In view of the other known hazards, such as changes in the structure of desoxyribonucleic acid, it is reasonable to adopt a much wider approach. For example, the uptake of radiostrontium in the shells of eggs of fowls should be easily and continuously assessable and relatable to the uptake by the bones.[2] Also the question of how far the uptake of radiostrontium by the soil may affect biological cells may be partly tackled by study of the invertebrates that are in effective contact with mountainous soils—e.g., earthworms which ingest and egest large quantities of soil. The possibility of mutations can be surveyed more rapidly in such invertebrates than in humans.

More immediate action, such as methods of removing radiostrontium from drinking water and diet of animals, may also be called for; and I would urge that the most pressing question is not concerned with leukæmia and geography but with what can be done *now* to decrease the chance of radiostrontium uptake by animals and humans.

Hard water is less likely to contain radiostrontium than soft water,[2] If follows that, other things being equal, people living in hard-water districts are less likely to accumulate radiostrontium than those living in soft-water districts. (This expectation is modified by another factor—the source of milk, dairy products, and vegetables consumed. These, if they come from a mountainous soft-water district, are likely to contain more radiostrontium than their equivalents from chalky hard-water districts.) "Insoluble" salts of calcium (e.g., calcium phosphate, calcium sulphate, or calcium carbonate) could be added to the soil and even to the diet of animals.[2] I would go further and suggest that drinking water should be filtered through columns of such materials (which are inexpensive) or through corresponding ion-exchange columns which will remove all the radiostrontium. For water in reservoirs this could be done easily by adding a layer of the insoluble salts to the filter bed, and this should be done particularly in mountainous districts.

Physical Biochemistry Research School,
Science Department,
South-West Essex Technical College,
Walthamstow, London, E.17. S. LEWIN.

SIR,—If Dr. Hargreaves' "breakdown" of leukæmia deaths over eleven years "proves" anything at all, it would be, surely, that dilute fallout is not only harmless, but actually good for you—at any rate in Brecon and Westmorland, if nowhere else. Granted that no such conclusions were specifically stated, the inference seems not entirely unreasonable.

However, it is pertinent to remember that after the first fission test on July 16, 1945, at Alamogordo, there followed 205 assorted nuclear explosions, with a total yield of some 90 megatons. Since by no means all of this considerable megatonnage was cycled into our food-chain after 1947, perhaps the real significance of the leukæmia trend will only become apparent from a comparison of the past fourteen years with an equal period immediately preceding 1945, in which year the figure of 22 per million shows an increase of about 30% over the 1931 figure of 16 per million, whereas by 1958 the figure of 56 per million shows an increase of approximately 150% over the rate in 1945. Furthermore, after the Windscale reactor accident, in the nearby town of Seascale (population 2000) there were 4 leukæmia deaths within the year. This is 36 times the national average. A freak? Or cause and effect?

Bilston, Staffs. PAUL HAMMET.

11. Ford, E. B. *Biol. Rev.* 1945, **20**, 73.
12. Lewin, S. *Lancet*, 1957, i, 1251.
13. Lewin, S. *Brit. vet. J.* 1957, **113**, 380.

SIR,—Dr. Hargreaves (Nov. 7), commenting on Dr. Phillips' figures, shows that the incidence of leukæmia in Cornwall has increased little according to the Registrar General's figures.

It may be of interest to comment on the trend of the disease in this county as shown by a survey of 196 cases which have been investigated here between 1948 and 1959. There is no evidence of an annual increase in the disease during this time; indeed the number of cases diagnosed may be falling. What is of interest is the increasing number of cases discovered in the aged and the falling incidence in the young. No case has been seen in a child under 5 years since 1954. The mean age of onset of leukæmia was as follows:

	1948-52	*1953-56*	*1957-58*
Acute	27 years	49 years	66 years
Chronic	59 years	64 years	70 years

Since the recognition of leukæmia as a disease of old age is comparatively recent the failure of the annual figures to show an increase is most satisfactory.

It is still not sufficiently realised that facilities for the diagnosis of acute leukæmia were rarely available in rural areas until after 1950 and it is among the acute cases that the rising incidence of the disease is found.

In view of the alarm that could be caused by Dr. Phillips' analysis of leukæmia deaths in certain western counties, the results of the survey in Cornwall should be reassuring, and it is hoped to publish these figures shortly.

West Cornwall Hospital, Penzance. EILEEN E. WOOD Hæmatologist, West Cornwall Clinical Area.

RENAL LESIONS IN RHEUMATOID DISEASE

SIR,—The non-articular lesions of rheumatoid arthritis have lately received increasing attention. Lesions of similar histological appearance to the rheumatoid nodule have been described in the synovial and serous membranes and the cusps of the cardiac valves; and perivascular inflammatory lesions have been reported in striated muscles, peripheral nerves, and tendon sheaths. Ocular lesions and pulmonary involvement have recently been recorded. These reports have added a new similarity between rheumatoid arthritis and the other " collagen diseases " in the systemic involvement in these diseases. Renal lesions are well known in acute disseminated lupus, polyarteritis nodosa, and scleroderma. This prompted us to search for lesions in the kidney in rheumatoid arthritis, and this is a preliminary report about 5 cases of rheumatoid arthritis in which needle biopsy of the kidney was performed.

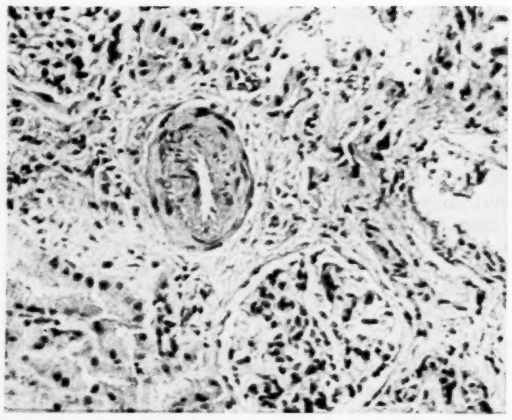

Fig. 1—Subendothelial thickening of interlobular artery and periarterial fibrosis. (×225.)

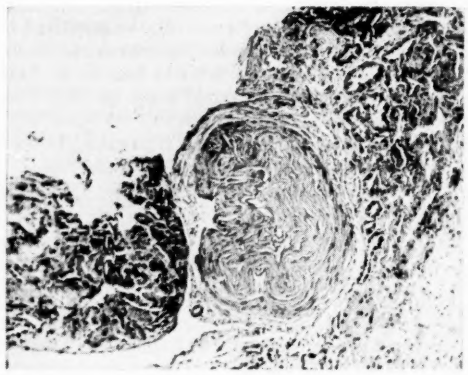

Fig. 2—Fibrous occlusion of interlobular renal artery. (×120.)

All 5 cases showed definite changes in the kidney. The main lesions were in the blood-vessels; the arteries of interlobular size showed subendothelial thickening of the intima (fig. 1), sometimes to a striking degree, with gross reduction of the lumen. Fibrous occlusion of the vessel was also noted in some cases (fig. 2). Perivascular cellular infiltration and perivascular fibrosis were often seen. Thirdly, cellular infiltration and fibrosis around the renal corpuscles was very common. The interstitial tissue as a whole showed greatly increased cellularity and fibrosis especially between the collecting tubules in the medullary rays of the kidney (fig. 3). Lastly, fibrinoid lesions were occasionally noted in the glomerular tufts.

Exactly similar lesions in the interlobular arteries were noted in scleroderma.[1–3] The perivascular cellular infiltration is similar to the periarteritis and the cellular infiltration in the adventitia and around the artery in polyarteritis nodosa. These findings strengthen Banks' suggestion[4] that polyarteritis nodosa, scleroderma, dermatomyositis, disseminated lupus erythematosus, and rheumatoid arthritis are related clinically and *pathologically*, and could be properly grouped as diffuse vascular and mesenchymal diseases, and may be referred to as the " collagen vascular diseases ".

Our study permits certain speculations and conclusions. Since there was no associated hypertension and no symp-

1. Moore, H. C., Sheehan, H. L. *Lancet*, 1952, i, 68.
2. Bartels, E. D., Christensen, L. K., Ohlsen, A. S. *Acta path. microbiol. scand.* 1955, suppl. 105, p. 174.
3. Calvert, H. J., Owen, T. K. *Lancet*, 1956, ii, 19.
4. Banks, P. M. *New Engl. J. Med.* 1941, **225**, 433.

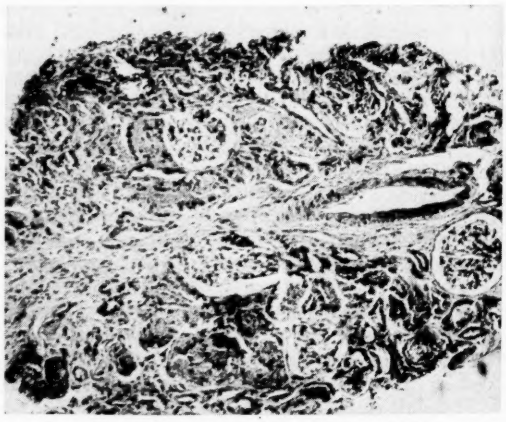

Fig. 3—Severe interstitial fibrosis. (×120.)

tom or history of renal disease, we attribute these renal lesions to the rheumatoid disease. In 2 of the 5 cases, the urine showed definite proteinuria and casts; in the other 3 cases, a trace of protein was found. Rheumatoid arthritis is well known to be complicated by amyloidosis when of sufficiently long duration. Proteinuria developing in a case of rheumatoid arthritis was empirically taken to indicate early amyloid change. This study points to the important fact that there are *other* genuine rheumatoid vascular and other renal lesions that may produce changes in the urine (and probably in renal function) besides amyloid degeneration, so that proteinuria developing in a patient with rheumatoid disease requires needle biopsy of the kidney to determine its exact cause.

Department of Medicine and the Renal Clinic, Abbassia Faculty of Medicine, Ein-Shams University, Cairo.

M. NAGY EL MAHALLAWY
M. S. SABOUR.

THE COCKETT/ELGAN JONES (ST. THOMAS'S) OPERATION

SIR,—Since 1954 I have used the Cockett/Elgan Jones operation for gravitational ulcers. A follow-up [1] of the results obtained by a combination of this operation with "stripping" of the varicose saphenous veins showed that all ulcers remained healed (1–4 years). Two ulcers treated by "stripping" alone recurred. Postoperative bandaging lasted 2–4 weeks.

In my opinion this operation is of paramount importance in our surgical treatment of venous leg ulcers, although in my experience all insufficient subcutaneous veins draining the ulcer region must be extirpated. The method of choice is thus "stripping" plus the Cockett/Elgan Jones operation.

Mariestad, Sweden. CARL C. ARNOLDI.

THE NATURE OF ESSENTIAL HYPERTENSION

SIR,—Analysing the problem of the nature of essential hypertension, Professor Platt (July 25) considers that "there seem to be at least two possible factors which may tend to obscure the facts when populations rather than individuals are studied. First, if it be true that essential hypertension is a disorder which manifests itself chiefly between the ages of 45 and 60, there must be younger ages at which the blood-pressure is rising at different rates and to varying degrees in different individuals." Professor Platt goes on to say that the rate of rise of pressure is a "complicating factor" when the distribution curves of blood-pressure are plotted against age.

Nevertheless, from a study of the rate of rise of pressure on age in a population sample,[2 3] we concluded that this "complicating" factor must be considered in any quantitative study of blood-pressure. Applying the equation of the regression line of pressure on age in a group of 231 apparently healthy "normotensive" men followed 12 years, we found that the rate of rise of pressure was 0·31 mm. per year between 20–49 years of age, and 1·06 mm. per year between 50–64 years of age. Thus, in the normotensive subjects the rate of rise of blood-pressure increases with advancing age.

To determine the rate of rise of pressure of normotensive subjects when they became "hypertensive" we studied a group of apparently healthy men who were normotensive at their first routine examination for employment and who at follow-up 11 years later had developed "essential hypertension".

MEAN DIASTOLIC BLOOD-PRESSURE (B.P.) (mm. Hg) AT ROUTINE EXAMINATION OF 86 APPARENTLY HEALTHY MEN WHO BECAME HYPERTENSIVE

Age-group (yr.)	Normotensive phase			Hypertensive phase		"Acceleration" (rate of rate of rise in pressure) (mm. per yr. per yr.)
	B.P. at first examination (*a*)	B.P. at last examination (*b*)	Rate of rise in pressure (mm. per yr.)	B.P. at first examination (*c*)	Rate of rise in pressure (mm. per yr.)	
30–49	85·5 (*33*)	89·8 (*39·7*)	0·64	113·1 (*43·6*)	5·9	0·98
50–69	86·5 (*46*)	90·0 (*50·4*)	0·78	113·7 (*57·1*)	3·5	0·49

Figures in parentheses denote mean age (yr.) at time of examination.

From a study of 10,000 case-records of both sexes we found that 86 men were hypertensive. In each case, three times in the evolution of the diastolic pressure were noted: (*a*) the first examination when "normotensive", (*b*) the last examination as "normotensive" (under 105 mm. Hg), and (*c*) the first examination as "hypertensive" (over 110 mm. Hg). The group was split into two, according to the age at which they became hypertensive: a younger group aged between 30 and 49, and an older one between 50 and 69.

The results (see table) show that in subjects who became hypertensive the rise in diastolic pressure in the younger men was at a significantly higher rate, and at a significantly higher acceleration, than in the older patients.

The quantitative component of blood-pressure has two factors: intensity or "height", and "rate of rise", of pressure.[4] The problem of the nature of essential hypertension has been explored only by means of the first factor; the "height" of pressure plotted against age. We think that a quantitative analysis should be performed considering both factors, and that the second factor, instead of obscuring the problem, will clarify it.

Aguirre Hospital, University of Chile School of Medicine, Santiago, Chile. R. CRUZ-COKE.

TOXIC CHEMICALS IN AGRICULTURE

SIR,—Mr. Whitehead's letter of Oct. 31 pinpoints the tragedy of the indiscriminate use of chemicals, and their ecological effects. What is so sad is that it has taken the death of one human being to bring to the fore the real dangers of a spray procedure which may well have caused the deaths of hundreds, if not thousands, of animals. Man's vanity of his own importance!

Pyford, Surrey. W. M. ALLCROFT.

REFORM OF THE LAW ON HOMOSEXUALITY

SIR,—No-one would disagree with Dr. Learoyd (Nov. 7) that homosexual seduction of the young must be prevented. However, there is no evidence that homosexuals are any more liable to commit this type of crime than heterosexuals; and it would require far stronger reasons than unsupported generalisation to justify the present law governing relations between adults. This disease can be difficult or impossible to cure, and it is surely mere common decency to allow those who are affected to lead their own lives as they think fit. The consequences of this law are often tragic, and the young can be effectively protected without it.

Manchester. G. E. G. WILLIAMS.

1. Arnoldi, C. C. *Danish med. Bull.* 1958, **5**, 272.
2. Cruz-Coke, R. *Rev. Med. Chile*, 1959, **87**, 116.
3. Cruz-Coke, R. *J. Amer. med. Ass.* 1959, **171**, 1333.
4. Cruz-Coke, R. *Lancet*, 1958, ii, 752.

Parliament

Deficit in N.H.S. Pension Scheme

IN a written answer Mr. DEREK WALKER-SMITH, the Minister of Health, made the following statement on the Government Actuary's report on the National Health Service superannuation scheme 1948–55 [1]:

The Government Actuary found that on March 31, 1955, there was a deficiency in the scheme of £79·5 million. Of this, £34 million was an initial deficiency attributable to decisions at the inception of the scheme to give recognition to the existing rights and expectations of those transferred to the National Health Service when it was set up, and to the entry into the scheme at that time of persons at ages above the normal ages of entry to the health service. About £40 million is attributable to rises in wages and salaries since 1948.

It is proposed that the deficiency should be dealt with as follows. The superannuation account will be credited with £34 million, representing the " initial deficiency ". An accounting adjustment will be made retrospectively from 1948 in order to meet the whole of the deficiency of £4·1 million arising from payments in respect of practitioners who maintain individual policies. Employees' contributions will not be increased, but in future interest will not be paid on contributions returned to employees who voluntarily leave the health service before becoming entitled to any superannuation benefit. It is estimated that this will produce a saving of about £0·9 million. The balance of the deficiency, namely, £40·5 million, will be liquidated over a period of approximately twenty years by adding to the present employer's contribution a special supplement of 1½% of salary.

The staff interests concerned are being informed and their observations invited prior to the laying of the necessary draft regulations before Parliament.

New Bills

New Bills introduced this session include the Population (Statistics) Bill, which was read for the first time in the House of Lords on Nov. 3. It amends and makes permanent the Act of 1938 and amends the particulars required for the registration of stillbirths.

Private members who have been successful in the ballot are to introduce the following Bills: a Bill to provide compensation for the victims of crimes of violence (Mr. Reginald Prentice); a noise abatement Bill (Mr. Rubert Speir); a Bill to implement the recommendations of the Gowers Committee for the improvement of conditions of work in offices (Mr. Richard Marsh); a Bill to abolish the earnings rule for widowed pensioners who have children to support (Mr. William Griffiths).

QUESTION TIME

Suicide While on Remand

Mr. CHARLES ROYLE asked the Home Secretary if his attention had been called to the suicide of a young man while on remand in prison; and what steps he proposed to take to ensure that a repetition of such a case shall be avoided.—Mr. DENNIS VOSPER, the parliamentary secretary, replied: The boy had been for six days in a room in Durham prison hospital because of an earlier attack of hysteria. He appeared to have completely recovered and, on the morning of his death, had asked to be discharged from the hospital. He ate well when the midday meal was served just before noon. He was found to be dead during a routine check at 12.35 P.M. The Minister is satisfied that no other steps could have been taken to prevent the suicide.

Mr. ROYLE: Will the Home Office go into the question of the great need for remand centres, which would save young people from being sent to prison on remand?—Mr. VOSPER: The Minister agrees about the great need for remand centres.

1. H.M. Stationery Office, 1959. Pp. 24. 1s. 9d.

Accommodation in Prisons

Mr. HENRY HYND asked the Home Secretary how many prisoners were now sleeping three to a cell; and what progress was being made towards ending such overcrowding.—Mr. VOSPER replied: On Oct. 20 there were 6642 men housed three to a cell. So long as committals remain at their present level, the only method of reducing this overcrowding is to provide extra accommodation, which the Minister is making every effort to do. Tenders have been accepted for one new security prison and planning clearance has been obtained for the building of a second, but it is to open prisons that we must look for speedy relief. Two of these have been opened in the past eighteen months and a further four are under construction.

Hospital Building

The following 6 new hospitals have been partially built and are in use:

Balderton Hall, near Newark (mental deficiency); Good Hope, Sutton Coldfield (general); Greaves Hall, Southport (mental deficiency); Princess Margaret, Swindon (general); Oakwood Park, near Conway (mental deficiency); and West Wales, Glangwili (general).

Work is in progress on the following 9 new hospitals:

Cambridge (teaching); Crawley (general); Harlow (general); Hensingham, W. Cumberland (general); Huddersfield (general); Sheffield (teaching); Welwyn-Hatfield (general); Llanfrechfa Grange, Newport (mental deficiency); Singleton Park, Swansea (general).

Work is expected to start on the following new hospitals in 1960–61:

Branch of Royal Marsden Hospital (teaching) at Sutton; Slough (general); St. Thomas's, London (teaching); and Truro (general).

Public Health

British Student Tuberculosis Foundation

THE several units of this Foundation have now been brought together to form a permanent centre at Pinewood Hospital, Wokingham, Berkshire, for the treatment and rehabilitation of students with tuberculosis.

Both men and women are admitted to the centre, which has 32 beds. Students may receive treatment there under the National Health Service while they continue their studies. The library has over 3000 books, including works of reference, and for convalescent patients there are even separate studies for private work. Tutors visit the students regularly and direct their work. Medical treatment is under the supervision of Dr. J. J. McCann, physician-superintendent of the hospital. Inquiries about admission should be sent to the secretary/administrator of the Foundation, Pinewood Hospital, Wokingham, Berkshire.

Infectious Diseases in England and Wales

Disease	Week ended October				
	3	10	17	24	31*
Diphtheria	2	1	5	6	2
Dysentery	503	529	460	564	465
Encephalitis:					
Infective	5	3	3	8	2
Postinfectious	1	3	2	1	3
Food-poisoning	269	230	248	179	195
Measles, excluding rubella	796	822	959	1019	1038
Meningococcal infection	11	23	21	15	13
Ophthalmia neonatorum	19	16	15	24	16
Paratyphoid fever	7	9	6	4	6
Pneumonia, primary or influenzal	174	219	252	187	207
Poliomyelitis:					
Paralytic	23	19	18	18	13
Non-paralytic	11	9	5	10	..
Puerperal pyrexia	195	211	216	210	203
Scarlet fever	606	869	918	948	980
Smallpox	..	..	..	..	..
Tuberculosis:					
Respiratory	366	396	424	474	438
Meninges and C.N.S.	3	5	5	7	5
Other	48	46	48	49	49
Typhoid fever	5	2	4	4	5
Whooping-cough	645	485	502	546	453

* Not including late returns.

Obituary

CHARLES GORDON IRWIN

M.B. Durh., F.R.C.S.E.

Mr. Charles Irwin was appointed surgeon in charge of the orthopædic department of the Royal Victoria Infirmary, Newcastle upon Tyne, when it was opened in 1933. He gave up a busy general surgical practice to give all his energy and enthusiasm to his department, and until he retired in June it remained his constant pride and joy.

He was born at Tynemouth and educated there and at Stramondgate House, Kendal. He began his medical studies at Durham University in 1912. They were interrupted during 1914 and 1915 by service in the ranks in the R.A.M.C., but he returned to graduate with honours in 1917. Afterwards he served again with the R.A.M.C. in East Africa, Egypt, and India. The orthopædic problems which remained after the war stimulated his interest in this specialty, and in 1919 he spent six months studying under Sir Robert Jones.

Irwin was appointed orthopædic surgeon to the Ministry of Pensions in Newcastle, and the following year he became surgical registrar to the Royal Victoria Infirmary. He quickly won a reputation as an outstanding general surgeon and was invited to join the staffs of the Tynemouth Infirmary, the Cameron Hospital at Hartlepool, and the Durham County Hospital. In 1928 he was appointed assistant honorary surgeon to the Royal Victoria Infirmary. During this phase as a general surgeon his primary interest remained in orthopædics, and, among his publications, an essay on *Growth of Bone and Bone Grafting* won the Heath prize in 1926.

In 1931 it was decided to build an orthopædic department at the Royal Victoria Infirmary, and he was appointed honorary surgeon in charge. Helped enormously by his energy and enthusiasm, the newly built 50-bed department was opened in 1933 and orthopædics was established as a separate entity in the North-east of England.

His other appointments included a lectureship in orthopædic surgery in the University of Durham, he had always had a great reputation as a clinical teacher. He also shared in the organisation of miners' rehabilitation centres in Britain, and was an adviser and consultant to this service in Northumberland and Durham. In 1948 he became adviser in orthopædics to the regional hospital board, and he was one of the original members of the medical appeal tribunals when they were set up in 1949. Besides these heavy commitments he ran a busy private practice and was recognised as an expert on medicolegal problems and as a lucid and reliable witness in court. From 1952 to 1953 he was vice-president of the British Orthopædic Association.

K. J. S. writes:

"Much could be said of Gordon Irwin's talents. His operating was sheer artistry. He ran a large and busy department without friction or apparent effort. To his juniors he was always a good counsellor and friend. Though conservative in his outlook and restrained in his judgment, his amazingly percipient mind was quick to receive and assess everything new so that he was always abreast of the times. In all personal matters he was well-disciplined; his punctuality was a constant source of embarrassment to his junior colleagues.

"Born in Tynemouth, for the rest of his life Northumberland was his to know and to love. He knew every twist and turn of every river and road, particularly the roads which led him to the Tweed or the Eden. He was an excellent shot and golfer but fishing outlived his other sporting loves. He was never happier than when encouraging a fumbling beginner to catch his first salmon. For many he will live in memory as a consummate artist on a river bank, or if the river were unproductive, his unbounded knowledge of local terrain and folk-lore retailed with his inimitable urbanity made a blank day feel like high summer and well spent. He was within casting distance of the Tweed when he died. Gordon's friends came from every walk of life, but one thing they had in common, his stories. Whether one walked a hospital ward or a river bank, always they were apt, they made a little more of heaven the daily drudge.

"An orthopædic surgeon of outstanding merit and ability, he will be greatly missed and as a man of many parts, excellent in each and possessing a personal charm greater than all, he will be mourned. In the haunts of men on sport and leisure bent a great companion is at rest."

ALEXANDER MILLER

M.B. Glasg., F.R.C.S.E., F.R.F.P.S.

Mr. Miller, visiting orthopædic surgeon to the Victoria Infirmary, Glasgow, died at his home in East Kilbride on Nov. 4.

He qualified from the University of Glasgow in 1928, and after holding house-appointments at the Victoria Infirmary in Glasgow and at the Shropshire Orthopædic Hospital he settled in practice in his chosen specialty in Glasgow. Beside his appointment at the Victoria Infirmary he was consulting orthopædic surgeon to Mearnskirk Hospital in Glasgow, Hairmyres Hospital at East Kilbride, Dumfries Royal Infirmary, and Uddingston rehabilitation centre. He was regional consultant in orthopædics for South-west Scotland.

T. H. N. writes:

"To all his colleagues at the Victoria Infirmary the death of Alexander Miller will mean the loss of a personality which added immeasurably to the development of the Victoria, not only in his own department, but in the hospital as a whole. This can be traced to his flair for securing the active cooperation of the many associations to which he belonged and of the influential bodies with which he had a well-grounded acquaintance. In turn, this flair for gaining results from his fellows was due to the dominant quality he always showed—steadfastness of purpose, untainted by the evanescent enthusiasms which defeat their objectives in other men.

"He always maintained that he himself had not the faculty for research, but he gave the strongest encouragement to those of his staff who showed a bent in this direction. He was a highly practical man, with a sound critical ability in the more unusual type of case, no doubt engendered by the unrivalled experience which fell his way while building up the orthopædic services south of the city during the past twenty years.

"In lay circles, he found relaxation especially in two pursuits —curling and an appreciation of the arts. In the former, he was an accomplished player and a formidable opponent. He was a member of the Arts Club in Glasgow and was so popular he could readily secure a good speaker for the occasional non-medical meeting of the Glasgow Southern Medical Society. Though he had not been feeling well for almost two years, his fortitude and determination were such that only in the last three months before his final illness did he drop from his usual high level of energetic application to all the calls on his personal and professional resources."

JOHN McILDOWIE HOPE SMELLIE

M.B. Edin.

Dr. John Smellie, who died on Oct. 31, was a Scotsman who had been in general practice in Liverpool since his Army service in the first world war.

He was a native of Lanarkshire and graduated M.B. from the University of Edinburgh in 1917. Soon afterwards he joined the R.A.M.C. and he served with the Mesopotamia Expeditionary Force. On demobilisation he settled in practice in Sefton Park.

W. M. B. and A. J. R. write:

"John Smellie was particularly kind to junior colleagues, and many young consultants owe more than just practice to him, since he never failed to have a wide variety of well-informed observations on all medical matters from ethics to detailed laboratory investigations. Whatever the subject, he took care to acquire correct information, and he was the first to apologise on the rare occasion that he was mistaken. He hated anything which was pompous, and had no time for those—however senior they might be—who treated his patients unkindly. He was an expert on photography, and would delight his friends at Christmas with prints from favourite negatives, meticulously made with an enlarger which he constructed himself. His enthusiasm for photography and rose-growing was matched by the time and energy he gave to the many committees on which he served. His shrewd, honest, and forthright opinions enhanced his professional standing over the years. His serenity in the face of his fatal illness, his interest in the action (and cost) of the drugs he was given, and his strong Christian beliefs will remain a vivid memory with those who were privileged to know him."

Dr. Smellie is survived by his wife, his son Dr. William Smellie, with whom he had been in partnership for eleven years, and two daughters who are also doctors.

Diary of the Week

NOV. 15 TO 21

Monday, 16th

POSTGRADUATE MEDICAL SCHOOL, Ducane Road, W.12
4 P.M. Prof. Alan Kekwick: Disorders of Fatty Tissues.

HUNTERIAN SOCIETY
8.30 P.M. (Apothecaries Hall, London, E.C.4.) Dr. Richard Asher, Mr. Guy Warrack (for); Dr. Harvey Flack, Mr. Wynford Vaughan-Thomas (against); That Education of the Public in Medical Matters is to be Deprecated.

UNIVERSITY OF ST. ANDREWS
4 P.M. (Department of Medicine, Queen's College, Dundee.) Mr. W. F. Walker and Dr. H. G. Morgan: Electrolyte Disturbances from Abdominal Operations.

Tuesday, 17th

ROYAL COLLEGE OF PHYSICIANS OF LONDON, Pall Mall East, S.W.1
5 P.M. Sir Kenneth Clark: Art and Society. (Lloyd-Roberts lecture.)

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Mr. R. L. Huckstep: Recent Advances in the Surgery of Typhoid Fever. (Hunterian lecture.)

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. C. E. Dalgliesh: Biochemical Aspects of Disorders of Aminoacid Metabolism.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, Paddington, W.2
5 P.M. Mr. Geoffrey Barber: Obstetrics in General Practice.

POSTGRADUATE MEDICAL SCHOOL
4 P.M. Dr. E. H. Belcher: Isotope Dilution Analysis.

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Dr. J. St. Clair Elkington: Carotid and Basilar Insufficiency.

INSTITUTE OF DERMATOLOGY, Lisle Street, W.C.2
5.30 P.M. Dr. G. C. Wells: Histochemistry of the Skin.

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM
5.15 P.M. (General Infirmary at Leeds.) Sir Charles Symonds: Observations on the Facilitation or Arrest of Epileptic Seizures.

UNIVERSITY OF LIVERPOOL
5.15 P.M. (New Medical School) Mr. R. I. Stirling: The Mutability of Living Bone. (Lady Jones lecture.)

Wednesday, 18th

UNIVERSITY OF LONDON
5.30 P.M. (King's College, Strand, W.C.2.) Prof. Alfred Gilman (New York): Pharmacological Basis of Diuretic Drug Therapy.

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
8.15 P.M. *General Practice.* Dr. Annis Gillie, Dr. T. N. Rudd, Dr. E. Beresford Davies: The Ageing Mind.

POSTGRADUATE MEDICAL SCHOOL
2 P.M. Prof. C. E. Dent: Balance Tests.

INSTITUTE OF DERMATOLOGY
5.30 P.M. Dr. J. A. Dudgeon: Virus Diseases.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Mr. T. Holmes Sellors: Pulmonary Stenosis.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
3.30 P.M. Dr. J. Greenwood Wilson: Work of the Port of London Health Authority.

LONDON AMATEUR BOXING ASSOCIATION
8 P.M. (British Railways Film Unit, 25, Savile Row, W.1.) Stress and the Adaptation Syndrome. (Film.)

HARVEIAN SOCIETY OF LONDON, 11, Chandos Street, W.1
8.15 P.M. Prof. Alexander Haddow: Chemotherapy of Cancer.

EUGENICS SOCIETY
5.30 P.M. (Royal Society, Burlington House, Piccadilly, W.1.) Dr. A. E. Mourant: Blood Groups in the Study of Human Populations.

QUAKER MEDICAL SOCIETY
8 P.M. (Friends House, Euston Road, N.W.1.) Mr. Robert Roaf: Death on the Roads—Do We Care? (Lister lecture.)

ROYAL FACULTY OF PHYSICIANS AND SURGEONS, 242, St. Vincent Street, Glasgow, C.2
5 P.M. Prof. Albert Hemingway: Pumps and Pressures. (Lock lecture.)

UNIVERSITY OF ST. ANDREWS
2.30 P.M. (Department of Medicine, Queen's College, Dundee.) Dr. H. G. Morgan: Metabolism of Calcium and Bone.

Thursday, 19th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Dr. L. W. Proger: Recent Additions to the Museum. (Erasmus Wilson demonstration.)

ROYAL SOCIETY OF MEDICINE
4.45 P.M. *Dermatology.* Mr. Henry Hobbs: Ocular Lesions after Chloroquin Therapy.

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine.) Dr. M. D. Milne: Clinical Aspects of Disorders of Aminoacid Metabolism.

POSTGRADUATE MEDICAL SCHOOL
4 P.M. Dr. T. Alper, Dr. M. Ebert, Dr. R. H. Thomlinson: Biological Effects of Radiation.

BRITISH INSTITUTE OF RADIOLOGY, 32, Welbeck Street, W.1
8 P.M. Dr. R. O. Murray: Skeletal Changes Associated with Steroid Therapy.

NUFFIELD ORTHOPÆDIC CENTRE
8.30 P.M. (Wingfield-Morris Orthopædic Hospital, Oxford.) Dr. A. Lichtwitz: Laboratory and Clinical Diagnosis of Generalised Osteopathies.

LIVERPOOL MEDICAL INSTITUTION, 114, Mount Pleasant, Liverpool, 3
8 P.M. Prof. L. J. Witts: The Small Intestine in Clinical Medicine.

HONYMAN GILLESPIE LECTURE
5 P.M. (University New Buildings, Teviot Place, Edinburgh, 8.) Mr. Eric Samuel: Radiology of Arterial Disease.

Friday, 20th

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Epidemiology and Preventive Medicine.* Prof. C. P. Beattie, Dr. J. K. A. Beverley, Dr. G. B. Ludlam: Epidemiology of Toxoplasmosis.
8.15 P.M. *Radiology.* Dr. Eric Samuel, Dr. Philip Keates: Use of Contrast Media in the Diagnosis of the Acute Abdomen. Mr. H. Dendy Moore: Radiology in the Acute Abdomen.

POSTGRADUATE MEDICAL SCHOOL
10 A.M. Mr. A. J. H. Rains: Biliary Calculus—a Review of Research.
4 P.M. Dr. J. F. Goodwin: Pulmonary Hypertension.

FACULTY OF RADIOLOGISTS
4.30 P.M. (Royal College of Surgeons of England.) Sir Charles Dodds: Reflections on Cancer Research. (Crookshank lecture.)

INSTITUTE OF LARYNGOLOGY AND OTOLOGY, 330, Gray's Inn Road, W.C.1
5.30 P.M. Dr. R. E. O. Williams: Epidemiology of Respiratory Infections in Hospitals.

INSTITUTE OF NEUROLOGY, NATIONAL HOSPITAL, Queen Square, W.C.1
4.45 P.M. Dr. Macdonald Critchley: Evolution of Man's Capacity for Language.

BRITISH TUBERCULOSIS ASSOCIATION
5 P.M. (26, Portland Place, W.1.) Dr. J. G. Scadding: On Keeping the Rules (Presidential address). Dr. Ian Sutherland: Present Scope for Preventing Tuberculosis by Vaccination of School Leavers.

PLYMOUTH MEDICAL SOCIETY
8.30 P.M. (Freedom Fields.) Lord Taylor: The Future of General Practice.

Appointments

EVANS, J. L., M.B. Lond., D.OBST., D.P.H.: deputy M.O.H. and school M.O., Swindon.

MCKENZIE, W. S., M.B. Cantab., F.R.C.S.: honorary consultant surgeon, E.N.T. department, French Hospital and Dispensary, London.

TATTERSALL, GILBERT, M.B. Dubl., D.P.H.: assistant M.O. and M.O.H., Nottinghamshire (East Retford).

Birmingham Regional Hospital Board:

BENNETT, R. J., M.B. Birm., F.R.C.S.: part-time consultant E.N.T. surgeon, Stoke-on-Trent group of hospitals.

CREWS, S. J., M.B. Cantab., F.R.C.S.E.: part-time consultant ophthalmologist, Birmingham and Midland Eye Hospital.

DATTA, P. K., M.B. Calcutta: senior casualty officer, Dudley and Stourbridge group of hospitals.

GRAVES, F. T., M.S. Lond., F.R.C.S.: part-time consultant surgeon, Stafford group of hospitals.

LANGTON, LEONARD, M.D. Leeds, M.R.C.P., F.F.R., D.M.R.D.: consultant radiologist, Birmingham (Dudley Road) group of hospitals.

MUNRO, S. S. F., M.B. Aberd., D.O.M.S.: part-time consultant ophthalmologist, Hereford group of hospitals.

RUBINSTEIN, KAZIMIERZ, M.D. Beirut, F.R.C.S.E., D.O.M.S.: part-time consultant ophthalmologist, Birmingham (Dudley Road), (Mental C), (Mental E), and (Sanatoria) groups of hospitals.

TOPLEY, ELIZABETH, M.D. Lond.: deputy director, regional blood transfusion service.

Manchester Regional Hospital Board:

BLISS, RAYMOND, M.B. Edin., D.A.: assistant anæsthetist (S.H.M.O.), Bolton and district group of hospitals.

EVANS, VINCENT, M.B. N.U.I., D.A.: assistant anæsthetist (S.H.M.O.), North Manchester group of hospitals.

HAJIKAKOU, C. S., M.B. Manc.: senior casualty officer, Rochdale and district group of hospitals.

SMITH, J. P., M.D. Manc.: consultant pathologist, Christie Hospital and Holt Radium Institute.

Notes and News

NEW MEDICAL SCHOOLS FOR THE UNITED STATES

THE United States is one of the world's most heavily doctored countries; but the output of physicians is not keeping up with the increase in population. Accordingly Surgeon General Leroy Burney, of the U.S. Public Health Service, asked for a report on medical education from a 22-member consultant group. The report, lately published,[1] says that the present ratio of doctors to population is the minimum needed to protect the health of the American people, and that the number of doctors (including medically trained osteopaths) graduating each year must increase from the present 7400 to 11,000 by 1975. To achieve this the committee recommends the expenditure of $1000 million over ten years to increase medical education; half this sum, says the committee, should be furnished by the federal Government and the rest by State Governments and private foundations. Existing schools should be expanded and 20–24 new schools built. The Surgeon General has declared his support for these recommendations.

SCOTTISH HEALTH SERVICES COUNCIL

THE 1958 report[2] of this Council has been held up by the dispute in the printing industry and by the dissolution of Parliament, but in fact the main part of its contents has already been published. The committee appointed to consider the application to Scotland of the recommendations of the Royal Commission on the Law relating to Mental Illness reported to the Council last year[3] and the committee which was the Scottish version of the Cranbrook Committee reported its findings on maternity services earlier this year.[4] Besides summarising these important reports the Council records that during 1958 a joint committee of the standing Medical Advisory Committee and the Hospital and Specialist Services Committee was invited to review the therapeutic, organisational, and training aspects of hospital catering.

MEDICAL REFERENCES

IN January the National Library of Medicine of the United States Department of Health, Education, and Welfare is to begin publishing a monthly *Index Medicus* which will replace the *Current List of Medical Literature*. The *Index* is to be bigger and better than the *Current List*, and it will use a new system of indexing articles. Each year its issues will be collated and will be published by the American Medical Association as the *Cumulative Index Medicus*. Together these monthly and annual issues will replace the *Quarterly Cumulative Index Medicus*, formerly published by the Association. Further particulars may be had from the United States Government Printing Office Division of Public Documents, Washington 25, D.C.

A SYNTHETIC PENICILLIN COMPOUND

Bristol Laboratories, of East Syracuse, N.Y., working in collaboration with the British Beecham Laboratories, have lately announced the production of the first synthetic penicillin for clinical use—potassium alphaphenoxyethyl penicillin, in which a synthetic side-chain has been added to the penicillin acid still produced by a mould. (Previous variants, such as phenoxymethyl penicillin, have been produced entirely from the mould; and though penicillin has been competely synthesised, such preparations have not been made for clinical use.) Preliminary trials are said to indicate that the new compound, which is given by mouth, achieves antibiotic levels in the bloodstream higher than other penicillin compounds, is less apt to produce allergic reactions (but the number of patients so far tested is small), and is more effective, dose for dose, in the treatment of infection by some strains that are partly resistant to other penicillin preparations.

1. See *New York Times*, Nov. 1, 1959.
2. H.M. Stationery Office. 1959. Pp. 22. 1*s*. 3*d*.
3. See *Lancet*, 1958, ii, 741.
4. See *ibid*. 1959, i, 463.

SHEFFIELD GENERAL HOSPITAL

ON Oct. 26 the Earl of Scarbrough opened a new X-ray department at this hospital to take the place of the old department which was brought into use in 1915, when a single tube, capable of dealing only with fractures, was installed in a disused day-room.

The new department is a building of one storey grouped around a central processing suite. Its three internal corridors are arranged in a U-shape, the X-ray rooms lying internally to the letter, and the other offices being grouped externally to it. The smallest X-ray room measures 16 ft. by 18 ft. and the largest—which is used for operative cardiovascular investigations—about 16 ft. by 24 ft. The main gastrointestinal room is equipped with a barium-kitchen, and there is a lavage-room in which patients can be given their preliminary cleansing enemas. A pair of swing-doors divides off the rooms reserved for radiological procedures which need surgical intervention and the use of anæsthetics. One is equipped for angiocardiography and another for urological work. Both of these rooms have antistatic flooring. The production of working drawings for the new department was interrupted so that account might be taken of the recommendations recently published by the Ministry of Health for protection against radiological hazards.

The consultant radiologist is Dr. E. K. Abbott. The architects were Sir John Burnet, Tait & Partners, London, in association with the architect of the Sheffield Regional Hospital Board, Mr. E. F. Wilson, A.R.I.B.A.

NEW RADIOTHERAPY DEPARTMENT AT PORTSMOUTH

ON Oct. 30 Sir Stanford Cade opened the new radiotherapy wards and departments at St. Mary's Hospital, Portsmouth.

These extensions and adaptations provide additional treatment rooms and 14 beds for inpatient treatment. Hitherto inpatients had to be admitted to beds in other wards of the hospital, but the new building will enable inpatient and outpatient services to be available in a single unit. It also houses Eldorado and Orbitron cobalt units.

The senior radiotherapist of the Portsmouth hospital group is Mr. Ralph Gunderson, F.R.C.S., F.F.R. The plans of the building were prepared by Mr. Thomas K. Makins, A.R.I.B.A., of Portsmouth, in collaboration with Mr. Stewart Kilgour, A.R.I.B.A., of the Wessex Regional Hospital Board.

AN INTERNATIONAL GERIATRIC JOURNAL

TILL now the only clinical journals of geriatrics have been American, and we welcome the new international journal,[1] *Gerontologia Clinica*, with its two British editors, Dr. E. Woodford Williams and Dr. A. N. Exton, which will offer a focus for British and European contributions to this important specialty. The articles are in English, but there are summaries in French and German and the contributors come from all over Europe.

The first number contains the proceedings of the first meeting of the European clinical section of the International Association of Gerontology which was held at Sunderland a year ago. Prof. E. Greppi and his team from Florence contribute studies of the coagulability of the blood and the use of anticoagulants in the aged. Dr. B. Prusik (Prague) discusses the problems of cardiac infarction in old age, and Dr. F. Verzar (Basle) describes the muscular changes of age in relation to those of muscular dystrophy. The British contributions include an article by Mr. J. R. Moore on the dental care of the geriatric patient. The most outstanding contribution is a review by Dr. H. M. Sinclair of nutrition in relation to ischæmic heart-disease.

HEART SURGERY IN RUSSIA

A Russian film called *For the Life of the Doomed* (16 mm., sound, black-and-white, 75 min.) is a popular exposition of cardiac surgery performed at the Institute of Chest Surgery of the U.S.S.R. Academy of Medicine and at other centres. It was under the supervision of Prof. Alexander Bakulev.

After a brief description of the physiology of the circulation and the effects of various cardiac lesions, a woman with mitral stenosis

1. *Gerontologia Clinica*. Editors: Dr. E. Woodford-Williams (General Hospital, Sunderland) and Dr. A. N. Exton-Smith (Whittington Hospital, Highgate Wing, Dartmouth Park Hill, London, N.19). Published quarterly by S. Karger Ltd., Arnold-Böcklin-Strasse, 25, Basle, Switzerland. Annual subscription: Sw. Fr. 38.50 or $9.25.

and two children, one with Fallot's tetrad and the other with pulmonary stenosis, are followed through their investigations and operations. Diagrams are used to explain the effects of mitral stenosis and the principle of valvotomy. A cinemicrographic sequence shows the development of a chick's heart, as an introduction to developmental defects and shunts in humans. A cardiac catheter is shown entering the left ventricle through the septum, and angiocardiography reveals a tetrad of Fallot. Operation is performed under hypothermia, and arterial anastomoses are completed in a matter of seconds with the aid of special rings. The girl with the pulmonary stenosis is said to be a bad risk and emphasis is laid on the least spectacular but most important part of a surgeon's job—deciding whether to operate. Diagrams explain the operation, and an instrument for excising stenosed tissue within the pulmonary vessel is demonstrated. During the operation the ventricle starts to fibrillate and an electric defibrillator is used. Recovery is slow, and it is feared that there may be some anoxic brain damage.

This is a fascinating film and, though the emphasis is on human rather than medical aspects, there has been no sacrifice of detail, and medical audiences cannot fail to be interested. The English commentary is pleasant and informative.

The same film is available in colour on 35 mm. only, and both films may be hired from Plato Films Ltd., 18, Greek Street, London, W.1.

University of Oxford

On Oct. 31 the degree of B.M. was conferred on N. de M. Rudolf.

University of Cambridge

On Oct. 31 the following degrees were conferred:

M.D.—H. G. L. Lloyd-Thomas.
M.B., B.Chir.—*Gerald Herbert.
M.B.—*J. S. Grimshaw, P. V. Hunt.
* By proxy.

University of Birmingham

Mr. V. S. Brookes and Mr. P. Dawson-Edwards have been appointed part-time lecturers in surgery, and Dr. W. H. P. Cant and Dr. C. G. Parsons part-time lecturers in pædiatrics and child health.

University of Glasgow

On Nov. 7 the degree of CH.M. was conferred on R. G. Main.

Royal College of Physicians of Edinburgh

Queen Elizabeth The Queen Mother, who is an honorary fellow of the college, dined privately with the president and fellows on Nov. 7. The college presented her with a silver rose bowl to commemorate the occasion. After dinner, she signed the promissory obligation and was presented by the president with a copy of the history of the college.

At a meeting held on Nov. 3 with Dr. A. Rae Gilchrist, the president, in the chair, the following were elected to the fellowship:

A. L. Agranat, Birendranath Banerjee, Krishna Saran Mathur, J. K. Drummond, T. McS. Wilson, Rangasamy Natarajan, James Williamson, Kenneth Rhaney, A. B. Sclare, W. J. Weston, J. S. Meredith, Betty E. A. Magill, M. F. G. Buchanan, Muriel M. McLean, A. T. Doig, Deb Prasana Basu, Thamboo John Danaraj, A. K. MacA. Macrae, Phillip Harris, A. G. Fergusson, W. M. Jamieson, D. J. M. Mackenzie, D. M. Douglas.

The following were elected to the membership:

J. D. Sutherland, M. B. Matthews, A. G. Bearn, Alexander Henderson, Satya Pal Gulati, Donald Gill, William Mackenzie, Jitendra Chandra Chatterji, F. I. Rackow, Bhavanath Mishra, Neville Rosedale, Janet L. Elder, Nazim Shafiq Ghabra, Shafiq Yusif Bokhari, Rathindra Nath Ghosh, Bandana Gupta, W. R. Parkes, George Palmer, Gnanasundaram Subramanian, Himatlal Durlabhji Tolia, Tarak Das Banerjee, G. Z. Cooper, Mohamed Abu Shoke, R. S. J. Simpson, Abdul Hafeez Akhtar, K. E. Ussher, Ahmed Sadek El Halfawy, Kollengode Ramaswamy Balasubramanian, A. R. May, Amar Nath Mehrotra, W. G. Wade, W. D. Alexander, Sudhir Chandra Bose, Mohd. Abu Zafar Mohydin, K. R. Mitchell, F. A. Rhodes, Reda Mohammed Shaher, P. P. Kendall, T. M. Chalmers, William Hamilton, Madhab Bandhu Bhattacharyya, J. D. Cormack, Mohammad Masuduzzaman, Asoke Kumar Chaudhuri, Joan P. Ingham, R. St. J. M. Butler, Karunasena Jagodage Nanayakkara, Anirudh Prasad Singh, Ved Bhushan Gupta, I. M. Lowit, Eurfil Rhys Davies, Kasturi Bai Malik, Subhash Chander, F. Torgbor Sai, D. M. O'Sullivan, Yelahanka Patlamma Rudrappa, Mohamed Sadek Sabour, Karam Singh, T. A. J. Dawson, Jean Langlands, J. L. James, Ved Parkash Gupta, Raghunandan Gaind, Michael Brown, Ludlow Montclair Burke, P. L. de la Harpe, Shyam Pratap Singh, Leonard Brenner, J. E. Thompson, Valerie J. Marrian, Stylianos Herodotov Nicolaides, G. R. Sutherland, Benjamin Gentin, Ananda Kali Sain, P. D. Marsden, Audrey A. Dawson, J. B. Dawson, Sahibzada Sheikh Naeeum-ul-Hamid, Christina M. Comty.

Royal Society

This society has awarded the Copley medal to Sir Macfarlane Burnet, director of the Walter and Eliza Hall Institute, Melbourne, for his contributions to knowledge of viruses and of immunology.

British Society for Immunology

This society will hold a symposium on persistence of immunity, on Friday and Saturday, Nov. 27 and 28, at the Wellcome Foundation, 183, Euston Road, London, N.W.1.

Heberden Society

The annual general meeting of this society will be held on Friday and Saturday, Dec. 4 and 5, at the Wellcome Foundation, Euston Road, London, N.W.1. Prof. Albert Neuberger will give the Heberden oration and his subject will be the proteins of connective tissue and their metabolism.

International Society of Geographical Pathology

This society will hold an international conference at the Royal College of Surgeons of England, Lincoln's Inn Fields, London, W.C.2, from June 28 to 30, 1960, under the presidency of Prof. J. H. Dible. The theme of the conference will be eclampsia and pre-eclampsia in pregnancy. The secretary of the British organising committee is Prof. J. S. Young, Department of Pathology, Foresterhill, Aberdeen.

Singapore Academy of Medicine

The following officers have been elected for the coming year:

Master, Dr. C. E. Field; assistant master, Dr. G. Haridas; scribe, Dr. Gwee Ah Leng; bursar, Dr. N. C. Sen Gupta; bedell, Mr. D. W. C. Gawne; censors, Prof. G. A. Ransome, Dr. Lim Kee Loo, Dr. J. W. Hoe, Dr. G. Keys Smith, Mr. Y. Cohen.

Dr. R. A. Hickling, Sir Stanley Davidson, and Prof. John Bruce have been elected honorary members.

Offer for Belfast Virus Laboratory

The National Fund for Poliomyelitis Research has offered a grant of £70,000 to the Queen's University, Belfast, towards the cost of building a virus laboratory. The total cost will be about £250,000. The grant has been offered on condition that the university and the Northern Ireland Hospitals' Authority also contribute to the building.

Colonel C. H. Imrie has been appointed honorary surgeon to the Queen in succession to Colonel A. H. Charles.

Mr. E. A. Nicoll and Dr. Alan Hardy left England on Nov. 12 for a tour of Scandinavia. They will address the Danish Orthopædic Association in Copenhagen and afterwards will lecture in Stockholm, Upsala, and Oslo under the auspices of the British Council.

The Biochemical Society will hold a meeting on Saturday, Nov. 21, at 10.20 A.M., at Bedford College, London, N.W.1.

On Nov. 5 some 50 members of the Osler Club of London gave a dinner in honour of Dr. and Mrs. W. R. Bett. Dr. Bett, who is shortly taking up a post in the United States, was a co-founder of the club and for the past ten years has been its honorary secretary.

The medical group of the Royal Photographic Society is holding an exhibition at 16, Princes Gate, London, S.W.7, from Nov. 12 to 19 which will be opened by Dr. Hugh Clegg.

Mr. Kenneth Brill, of the Devon Children's Department, has written, at the invitation of the National Association for Mental Health, a booklet for people who wish to take foster children into their homes. He has called it *Room for More*, and copies (1*s.* 6*d.*) may be had from the Association, 39, Queen Anne Street, London, W.1.

Animal Behaviour, formerly the *British Journal of Animal Behaviour*, is the organ of the Association for the Study of Animal Behaviour, whose members include psychologists, physiologists, and other doctors, as well as zoologists. Its sixth volume appeared in an enlarged form made possible by linking up with the Section of Animal Behavior and Sociobiology of the Ecological Society of America. The journal is published twice yearly by Baillière, Tindall, & Cox, price £2 10*s.* for the two issues.